Multiple Myeloma: Current and Emerging Therapies

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Conflict of Interest

Principal Investigator Role: none
Employee: none
Consultant: Takeda, Bristol Myers Squibb
Major Stockholder: none
Speakers Bureau: none
Scientific Advisory Board: C4 Therapeutics, Oncopep

Integration of Novel Therapy Into Myeloma Management

Proteasome inhibitors: Bortezomib, carfilzomib, ixazomib; **immunomodulatory drugs:** thalidomide, lenalidomide, pomalidomide; **HDAC inhibitor:** panobinostat; **monoclonal antibodies:** elotuzumab and daratumumab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

20 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to 8-10 years.

Active MM (IMWG)

Hypercalcemia Renal Dysfunction Anemia Bone Disease (CRAB)

Even without CRAB features, the following events define active MM:

- **Bone marrow plasmacytosis ≥ 60%**
- **Abnormal FLC ratio ≥ 100 (involved kappa) or <0.01 (involved lambda)**
- **Focal bone marrow lesions on PET-CT and/or MRI**

Standard of care for smoldering MM is followup every three months. Protocols are evaluating novel agents and immune therapies to delay or prevent progression of smoldering to active MM.

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548

Risk of Progression of Smoldering to Active MM

		% Progressing to Symptomatic MM		
	3 Criteria:	1/3 Criteria (Low risk)	2/3 Criteria (Intermediate risk)	3/3 Criteria (High risk)
Mayo Clinic[3]	1. M-protein ≥3 g/dL 2. ≥10% clonal bone marrow plasma cells 3. Free light-chain <0.125 or >8	25%	51%	76%
	2 Criteria:	0/2 Criteria (Low risk)	1/2 Criteria (Intermediate risk)	2/2 Criteria (High risk)
PETHEMA[4]	1. ≥95% abnormal plasma cells 2. Low uninvolved serum immunoglobulins	4%	46%	72%

1. Rajkumar SV, et al. *Blood*. 2015;125:3069-75.
2. Landgren O, et al. *Blood.* 2009;1139:5412-17
3. Dispenzieri A, et al. *Blood*. 2008;111:785-9.4.
4. Pérez-Persona E, et al. *Blood*. 2007;110:2586-92.

SMM, smoldering multiple myeloma; MM, multiple myeloma.

Vaccines Targeting Specific Peptides to Delay Progression of Smoldering to Active Myeloma

- **Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses**

Clinical trials (LLS TAP Program):

Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

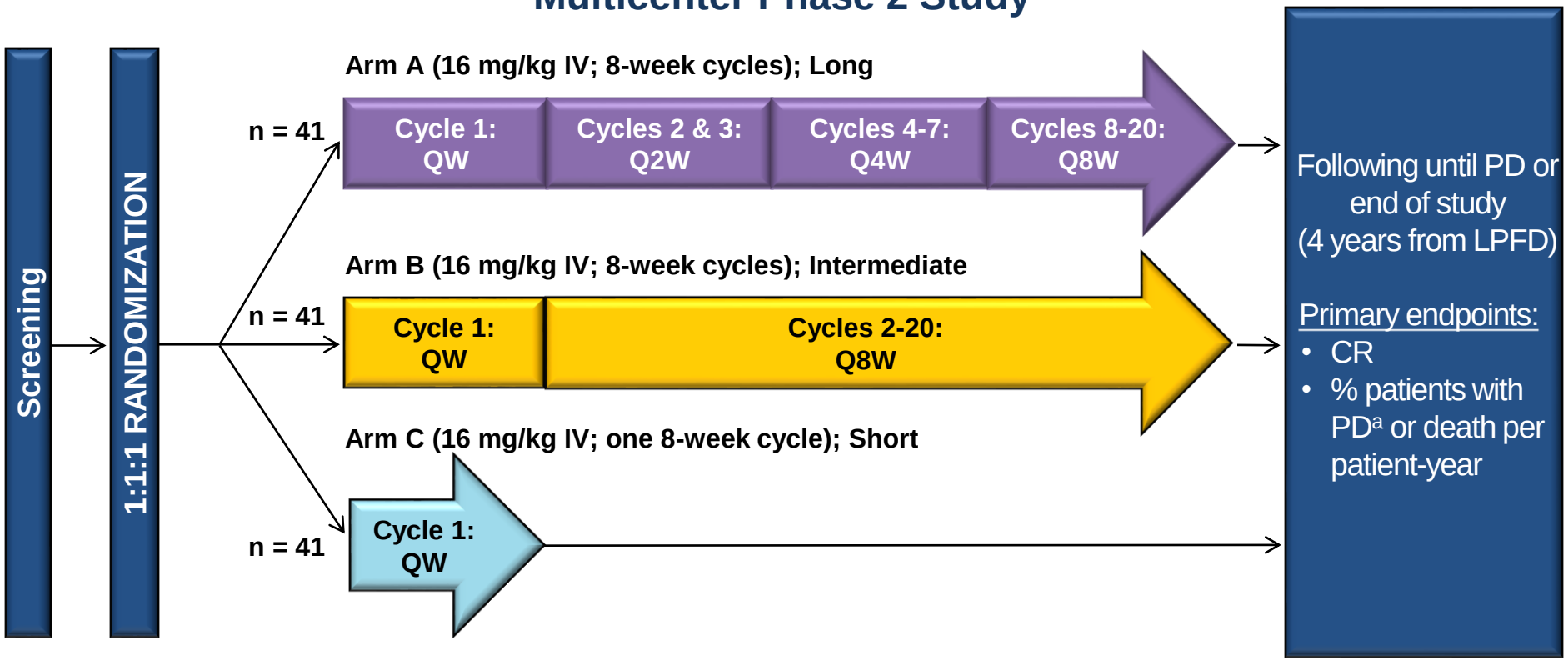
Lenalidomide with vaccine augments these immune response

(5 of 12 pts progressed to active MM with vaccine; only 1 of 9 pts progressed to active MM with vaccine + len)

Lenalidomide, PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Clin Can Res 2012; 17:4850-60.
Bae et al, Leukemia 2015
Bae et al Leukemia 2017

Daratumumab Monotherapy For Patients With Intermediate or High-risk Smoldering Multiple Myeloma (SMM): CENTAURUS, a Randomized, Open-label, Multicenter Phase 2 Study



[a]As defined by 2014 IMWG criteria for SMM.

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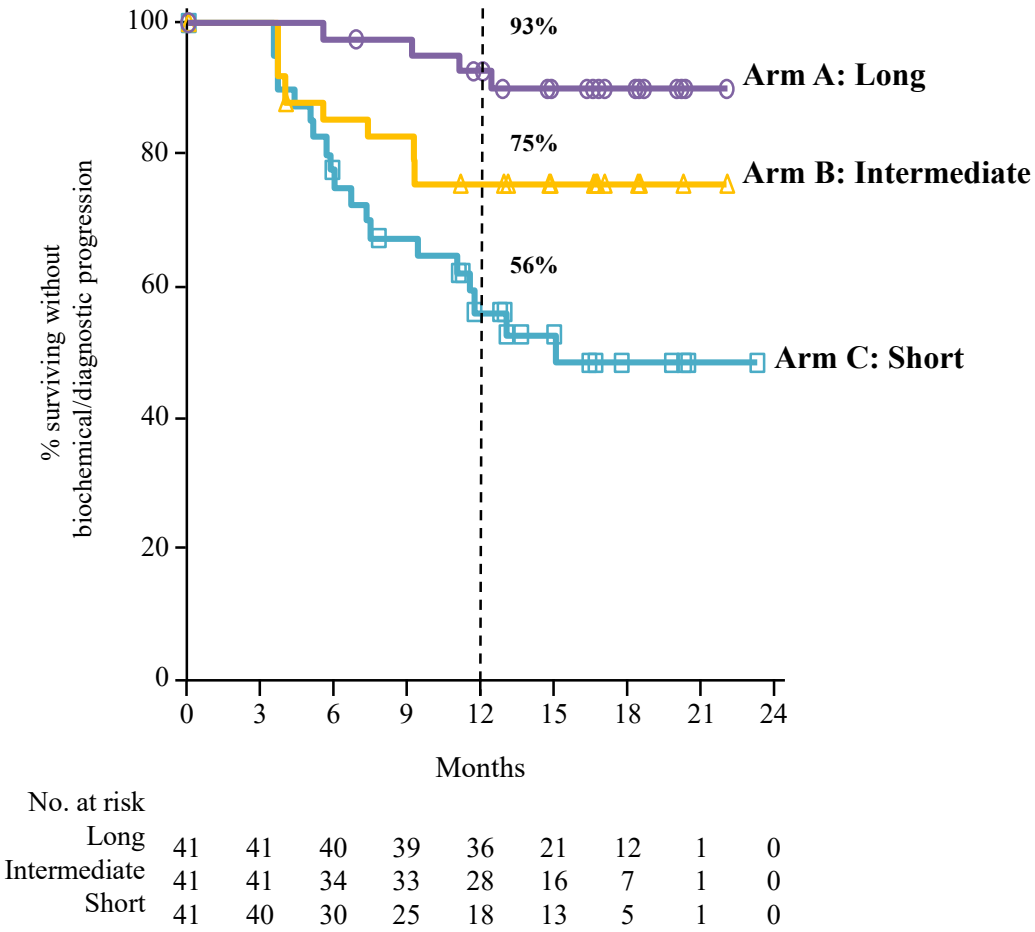
Hofmeister et al, ASH 2017

IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; PD, progressive disease; LPFD, last patient, first dose; CR, complete response.

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

CENTAURUS: PFS (Biochemical or Diagnostic)

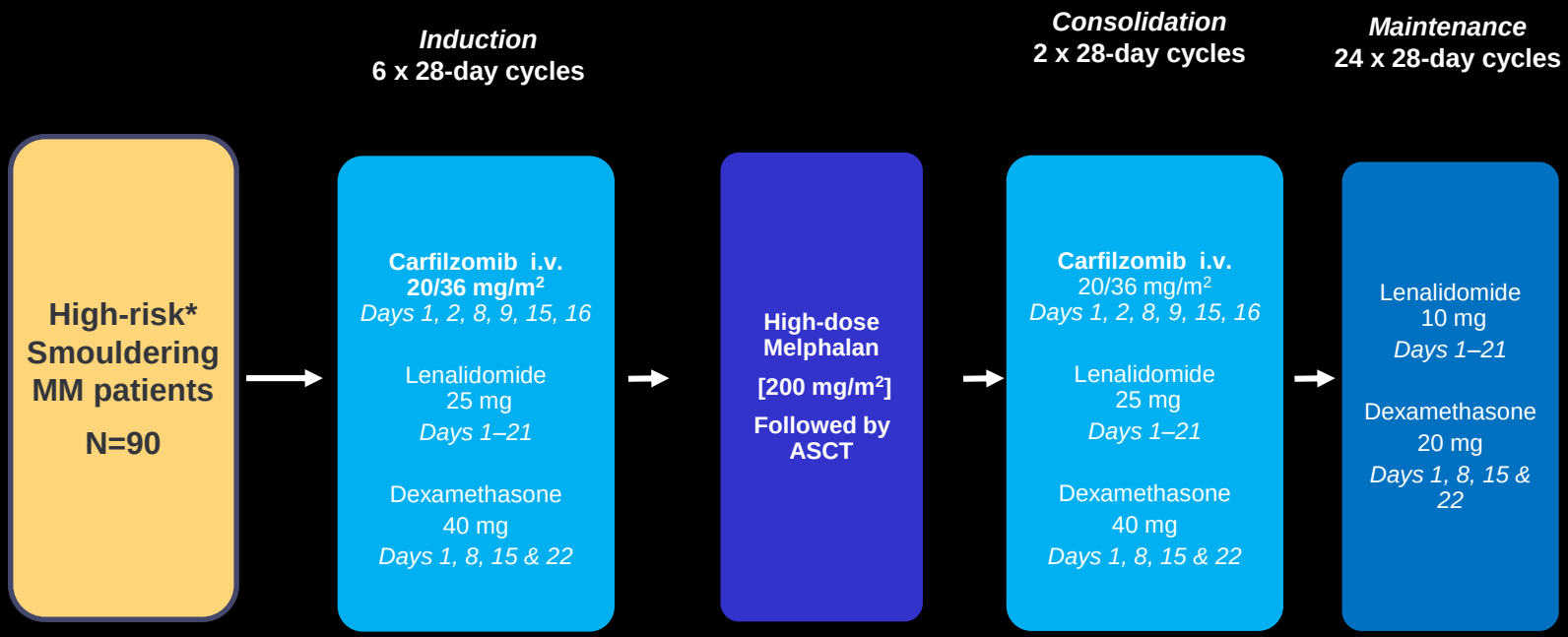


- Biochemical/diagnostic PFS is defined as the earlier of time to biochemical or diagnostic progression or death
  - Biochemical progression: measurable disease increase from nadir by ≥25% in 2 subsequent assessments per IMWG[1]
  - Diagnostic progression: SLiM-CRAB criteria
- Post-hoc analysis comparing Arm A + Arm B versus Arm C: *P* value = 0.0002

Hofmeister et al ASH 2017

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

Carfilzomib, lenalidomide dexamethasone (KRd), HDT-ASCT, KRd consolidation, Rd maintenance



*High-risk SMM was defined according to the Mayo and/or Spanish models

Mateos et al ASH 2017

GEM-CESAR:
Improved quality of response with treatment (n=35)

	Induction (KRdx6) N = 35	HDT/ASCT N = 35	Consolidation (KRdx2) N = 35
≥CR	**49%**	**62%**	**74%**
VGPR	37%	23%	20%
PR	14%	14%	6%
MRD-negative	**26%**	**47%**	**62%**

Mateos et al ASH 2017

International Staging System (ISS) for Myeloma

Stage	Criteria	Median Survival (mo)
I	β2m < 3.5 mg/L albumin ≥ 3.5 g/dL	62
II*	Not stage I or III	44
III	β2m > 5.5 mg/L	29

*β2m < 3.5 mg/L and albumin < 3.5 g/dL or
β2m 3.5 - < 5.5 mg/dL, any albumin

Greipp et al. J Clin Oncol 2005; 23: 3412-20

Revised ISS (R-ISS) incorporates LDH and high risk FISH abnormalities

Palumbo et all J Clin Oncol 2015: 33: 2863-9.

Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose theapy:

Nonhyperdiploid worse prognosis than hyperdiploid

t(11;14), hyperdiplody -standard risk

t(4;14), t(14;16),t(14;20), del(17p), del(13q14)- high risk

For novel treatments

Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)-

del(17p) p53 remains high risk

International Myeloma Working Group (IMWG) Criteria for MRD

- MRD Negative: Absence of aberrant clonal plasma in bone marrow aspirate , ruled out by an assay with minimum sensitivity of $1:10^5$ nucleated cells or higher (*i.e.*, 10^{-5} sensitivity)* Current methods are flow cytometry or NGS.
- Sustained MRD- negative: MRD negativity in the marrow (Flow or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart.
- Imaging plus MRD-negative: MRD negativity as defined by Flow or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

  - Kumar et al., Lancet Oncol 2016; 17: 328-46.

Initial Therapy for Newly Diagnosed MM

Transplant candidates (several cycles)

Triplets preferred: Lenalidomide/ Dex/Bortezomib (RVD) or Cyclophosphamide/Bortezomib/Dex (CyBorD)

Kyrpolis RD (KRD) if neuropathy.

Doublets rarely used, ie Bort/Dex to improve renal dysfunction, then add Len

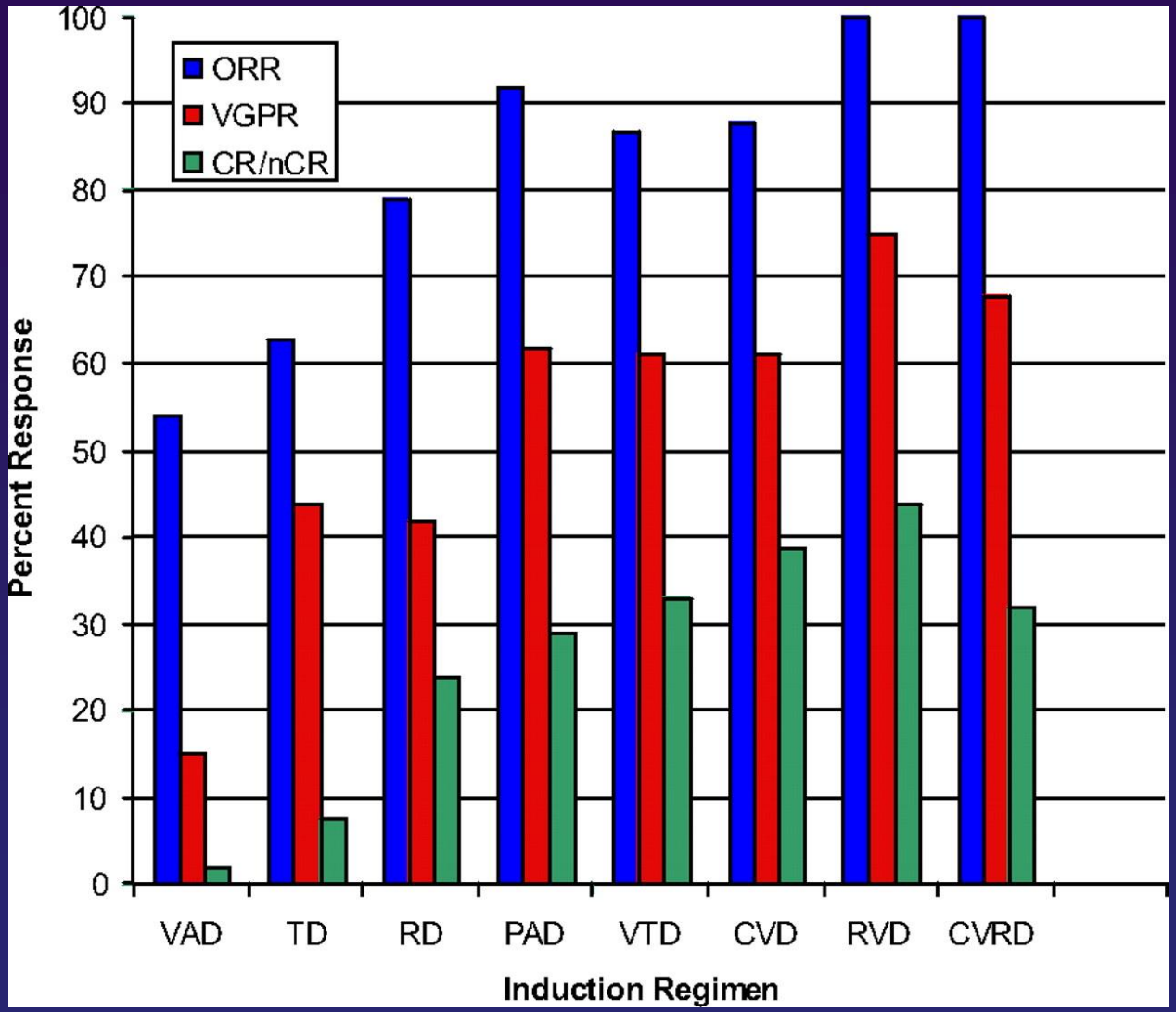
Maintenance Len in standard risk, Bort or Len Bort in high risk

Transplant ineligible (until progression)

Triplets preferred RVD, CyBorD, KRD but at reduced doses. Ixazomib Len Dex all oral regimen.

Doublets only in frail patients RD, VD at reduced doses

Combinations in the Upfront Treatment of MM



Stewart AK, Richardson PG, San Miguel JF Blood 2009

Daratumumab (DARA) With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Newly Diagnosed Multiple Myeloma: Updated Results of Phase 1b Study

Treated for up to 13 cycles (28 days/cycle) or until elective discontinuation for ASCT

- **Daratumumab 16 mg/kg (intravenous) was administered weekly (Days 1, 8, 15, and 22) during Cycles 1 and 2, every 2 weeks (Days 1 and 15) during Cycles 3 to 6, and every 4 weeks thereafter**
  - All patients received the first dose of daratumumab as a split dose over 2 days: 8 mg/kg on Days 1 and 2 of Cycle 1
- **Carfilzomib was administered weekly on Days 1, 8, and 15 of each 28-day cycle as a 30-minute infusion**
  - Patients received an initial dose of 20 mg/m2 on Cycle 1 Day 1 and escalated to 70 mg/m^2 at Cycle 1 Day 8+ if deemed tolerable
- **Lenalidomide was given at a dose of 25 mg on Days 1 through 21 of each cycle**
- **Dexamethasone was administered at a dose of 40 mg per week in patients aged ≤75 years and at a dose of 20 mg per week in patients >75 years of age**

Chari et al, ASH 2017

Conclusions

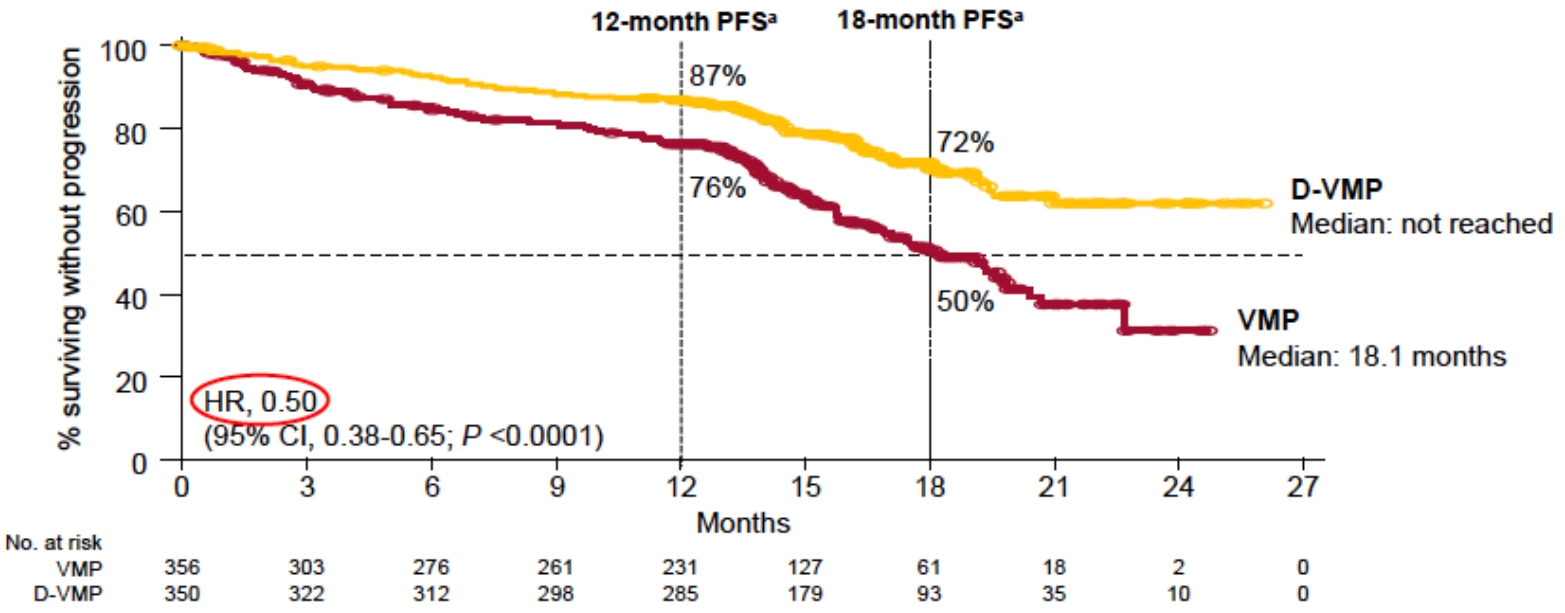
- **Daratumumab plus KRd is highly effective, with a 100% ORR, including 91% of patients with ≥VGPR and 57% of patients with ≥CR**
  - Depth of response deepens with longer follow-up
  - **MRD-negative rate at 10^{-5} was 14%**
- **Daratumumab with KRd was well tolerated**
  - safety profile is consistent with daratumumab and KRd
- **There was no adverse impact on stem cell collection (median $CD34^+$ 10.6×10^6 cells/kg)**
  - Daratumumab is feasible as part of induction therapy
  - Deep responses (3 sCRs; 3 VGPRs) were achieved prior to stem cell harvest
  - As responses were not assessed following stem cell transplantation, further deepening of responses induced by daratumumab plus KRd could not be captured in patients electing ASCT

Chari et al, ASH 2017

Daratumumab plus bortezomib melphalan prednisone (D-VMP) versus VMP in newly diagnosed transplant ineligible MM

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

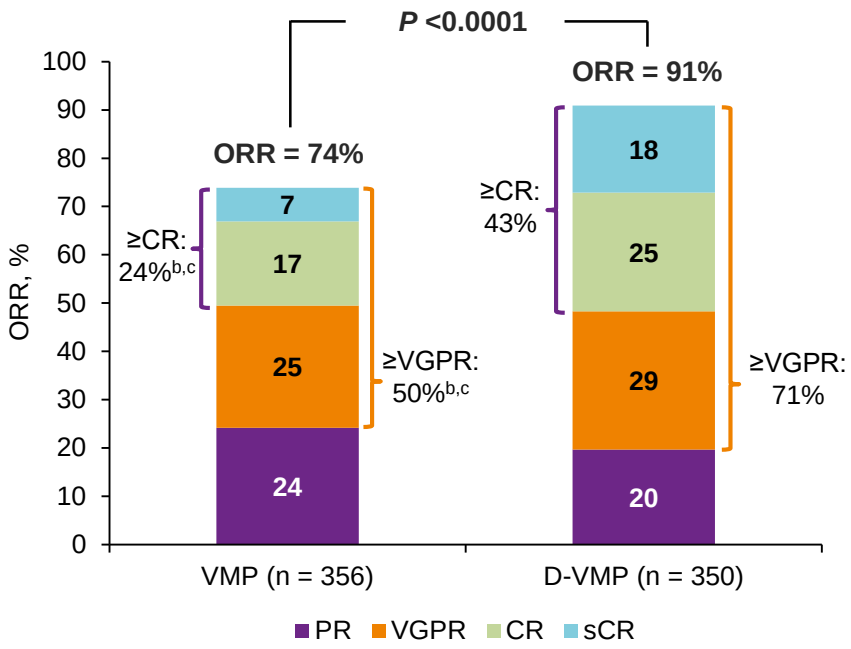


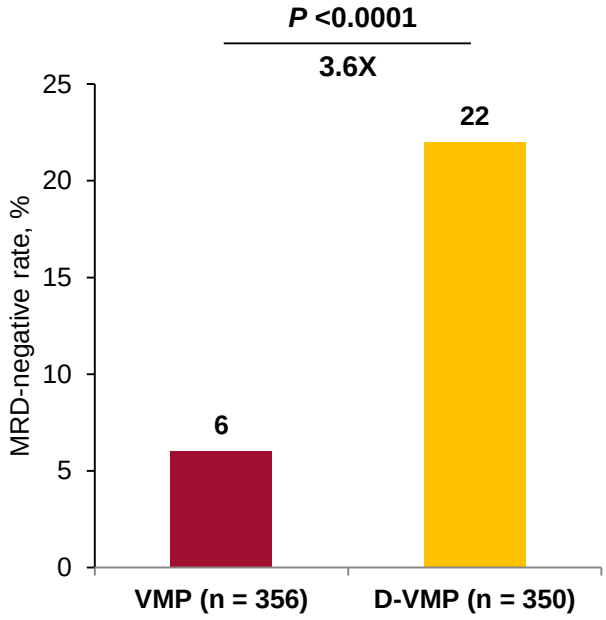
50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Mateos et al ASH 2017

DARA + VMP vs. VMP ~ Efficacy: ORR and MRD (NGS; 10^{-5} Threshold)





Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

Mateos et al ASH 2017

IFM: RVD and Early vs Late ASCT

	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al NEJM 2017; 376: 1311-20

MRD in Multiple Myeloma: Final Analysis IFM2009 Trial

Sensitivity (10^{-6}) (next generation sequencing) predicts better outcome: PFS and OS in both RVD and RVD ASCT arms, including both standard and high risk patients

Requirement to include MRD in all the upcoming trials

MRD could become the primary endpoint of future trials

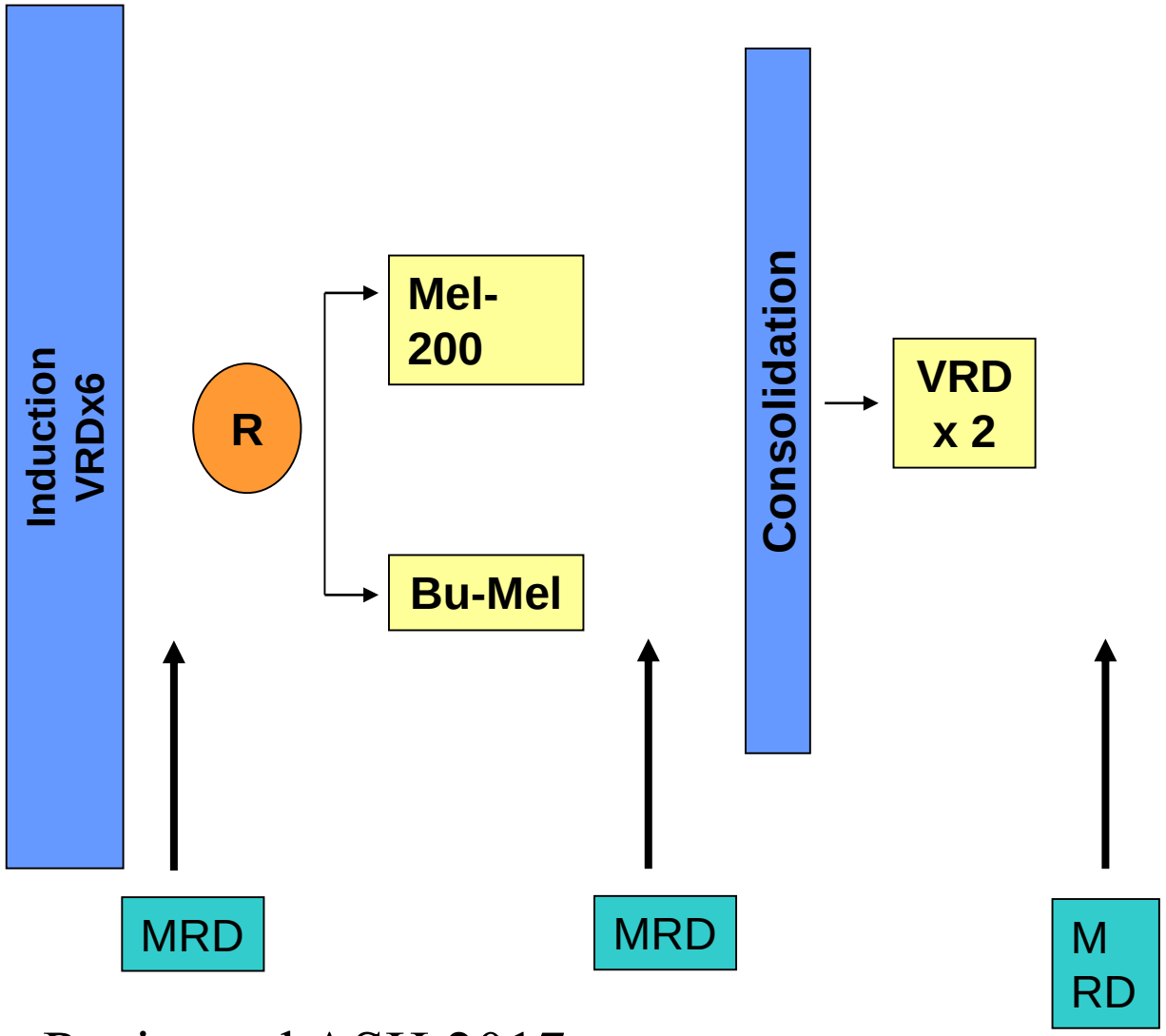
MRD will be central in the definition of cure

MRD will be essential to stratify patients:

- **consolidation randomization?**
- **maintenance randomization?**
- **maintenance duration?**
- **earlier définition of molecular relapses?**

Avet-loiseau et al, ASH 2017

GEM2012MENOS65: Study Design



Pavia et al ASH 2017

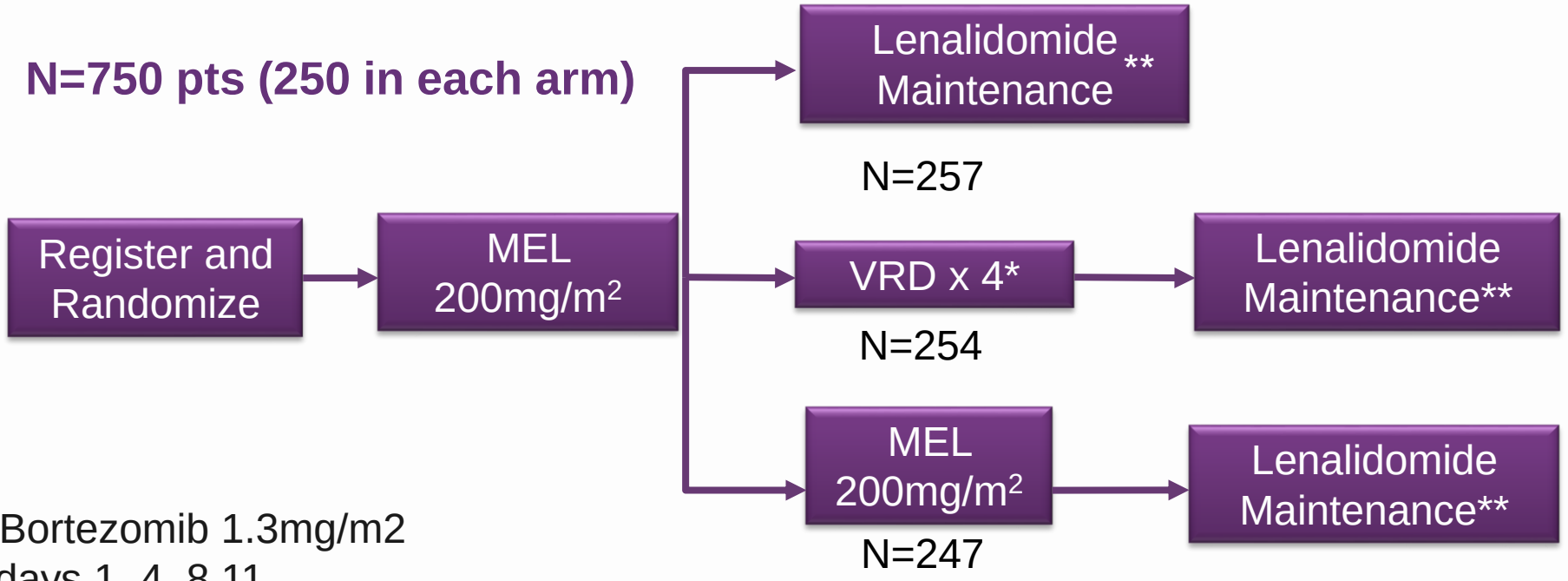
Rosiñol L, et al. ASH 2017; abstract 2017

Conclusions

- NGF (next generation flow cytometry) is feasible in large multicenter clinical trials (n=1,134), allows the identification of hemodiluted BM samples inadequate for MRD assessment, and is highly-sensitive
- MRD levels as low as 10^{-5} and 10^{-6} conferred significantly inferior PFS
- Risk of relapse among MRD-negative patients was remarkably reduced (3%), and was particularly associated with bone-related plasmacytomas
- **Overall, MRD-negativity is the most relevant clinical endpoint for both standard- and high-risk transplant-eligible MM patients**

Pavia et al ASH 2017

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

Stadtmauer et al ASH 2016

BMT CTN 0702 (STAMiNA) Summary

Largest randomized comparison of post transplant approaches in myeloma in the United States

Demographics well balanced among auto/auto, auto/RVD, auto/maintenance

At 38 months follow-up no difference in OS:
Auto/auto 82%, auto/RVD 85.7%, auto/maint 83.4%

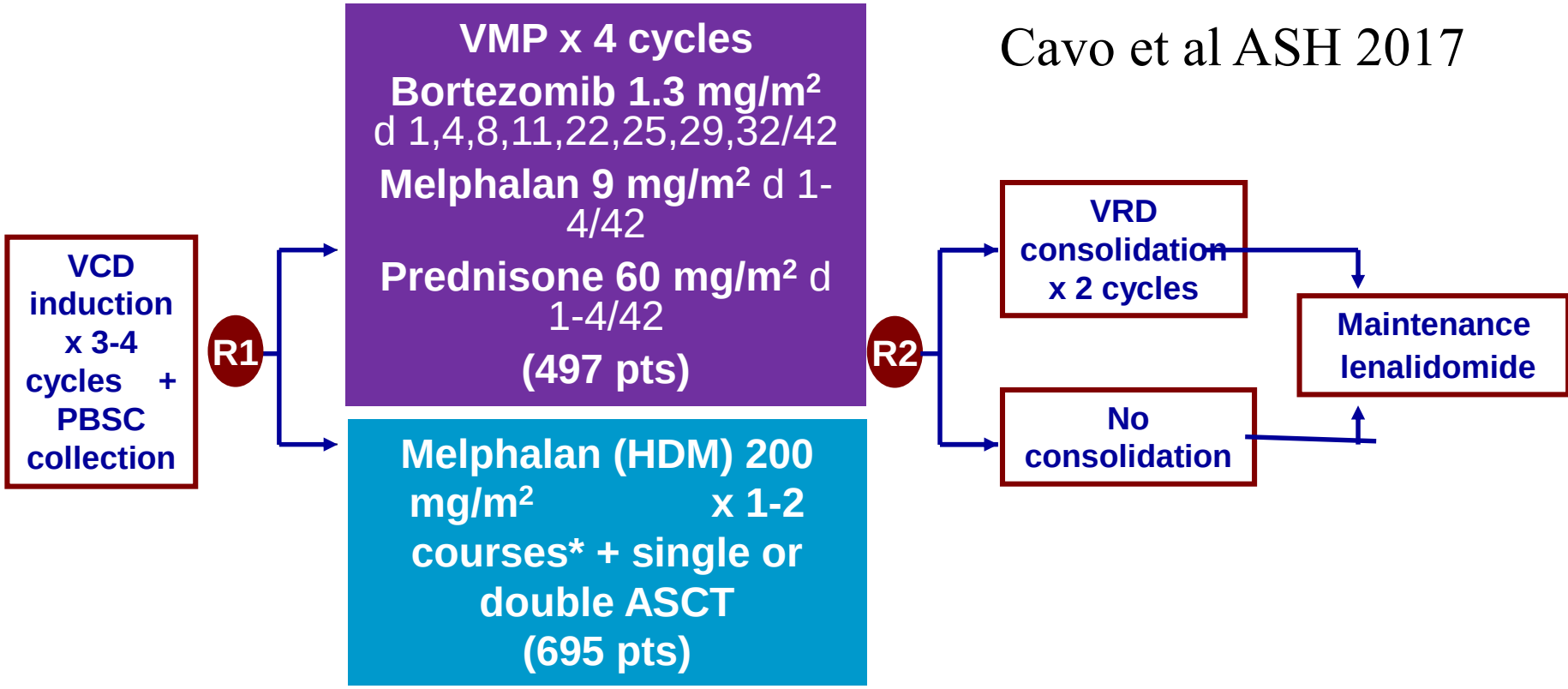
At 38 months follow-up no difference in PFS:
Auto/auto 56.5%, auto/RVD 56.7%, auto/maint 52.2% (high-risk wose than standard risk, but no difference by treatment arm)

Cumulative incidence of first secondary malignancy in the first 38 months similar for all 3 arms
5.9% (95% CI: 3.3%, 9.6%) in the Auto/Auto arm
6.0% (95% CI: 3.4%, 9.6%) in the Auto/RVD arm
4.0% (1.9%, 7.2%) in the Auto/Maintenance arm

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Stadtmauer et al, ASH 2016

EMN02/HO95 MM Trial Design



Cavo et al ASH 2017

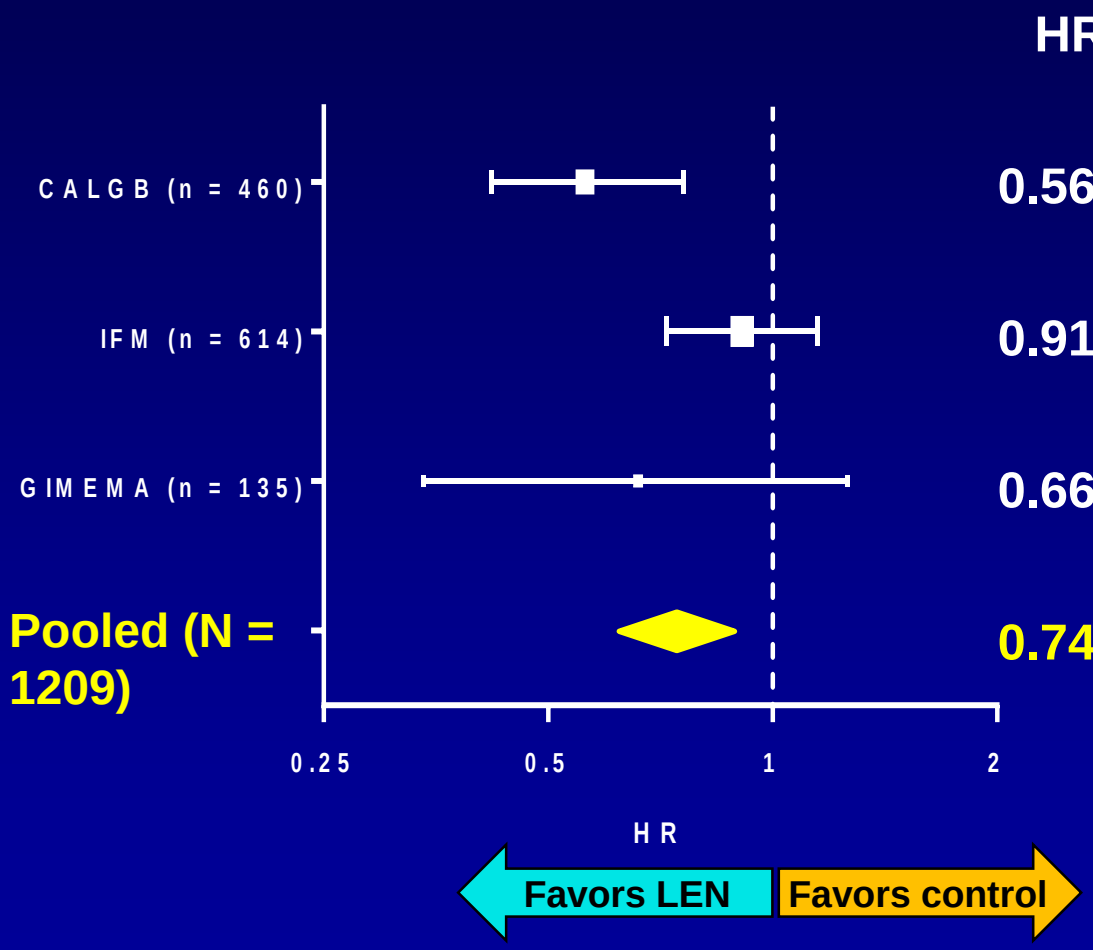
- **Stratification according to center and ISS disease stage (I vs. II vs. III)**
- **Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy**
- **Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy**

Conclusions

- Upfront ASCT was associated with a significant improvement in PFS and ≥VGPR as compared to VMP across subgroups of patients at low and high risk
- No OS difference between the two treatment groups was seen in the overall patient population, but OS was prolonged in patients at high risk
- Upfront double ASCT was associated with a significant improvement in PFS and OS as compared to single ASCT in the overall patient population
- Double ASCT overcame the adverse prognosis imparted by high risk cytogenetic abnormalities

Cavo et al ASH 2017

Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival Leading to FDA Approval



Attal et al ASCO 2016

- The size of the box is related to the size of the individual study. The confidence interval is a function of the overall sample size. HR, hazard ratio.

Maintenance Therapy Post-Transplant with Lenalidomide, Bortezomib and Dexamethasone (RVD) in High Risk Patients

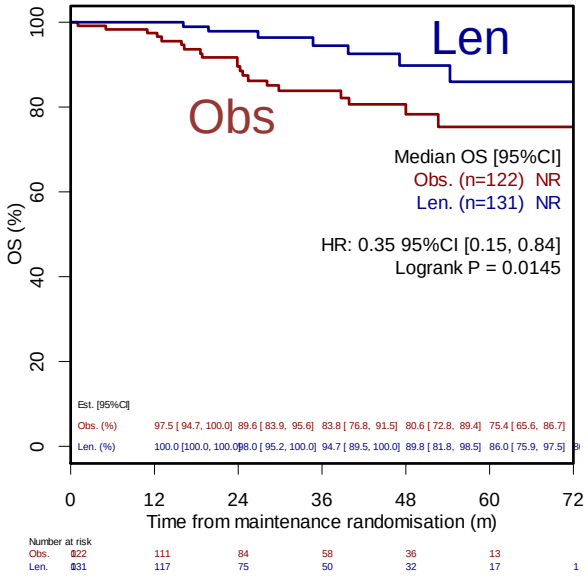
1. Stringent CR 51%, 96% VGPR
2. Median PFS 32 months
3. Three year OS 93%

Incorporate both lenalidomide and bortezomib in maintenance therapy of high risk MM.

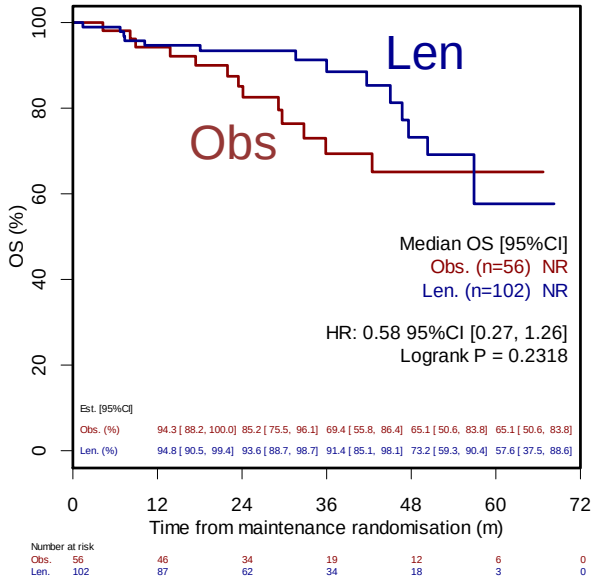
Nooka et al, Leukemia 2014: 28: 690-3.

MRC IX Transplant Eligible: Lenalidomide Improved OS Irrespective of Cytogenetic Risk

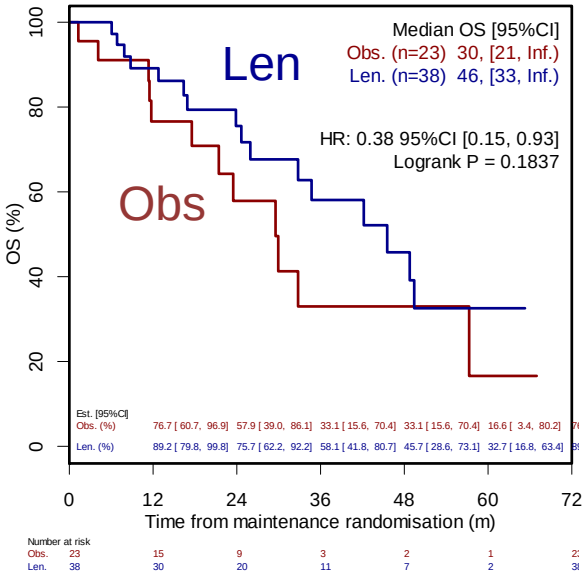
Standard risk: HR 0.35



High risk: HR 0.58



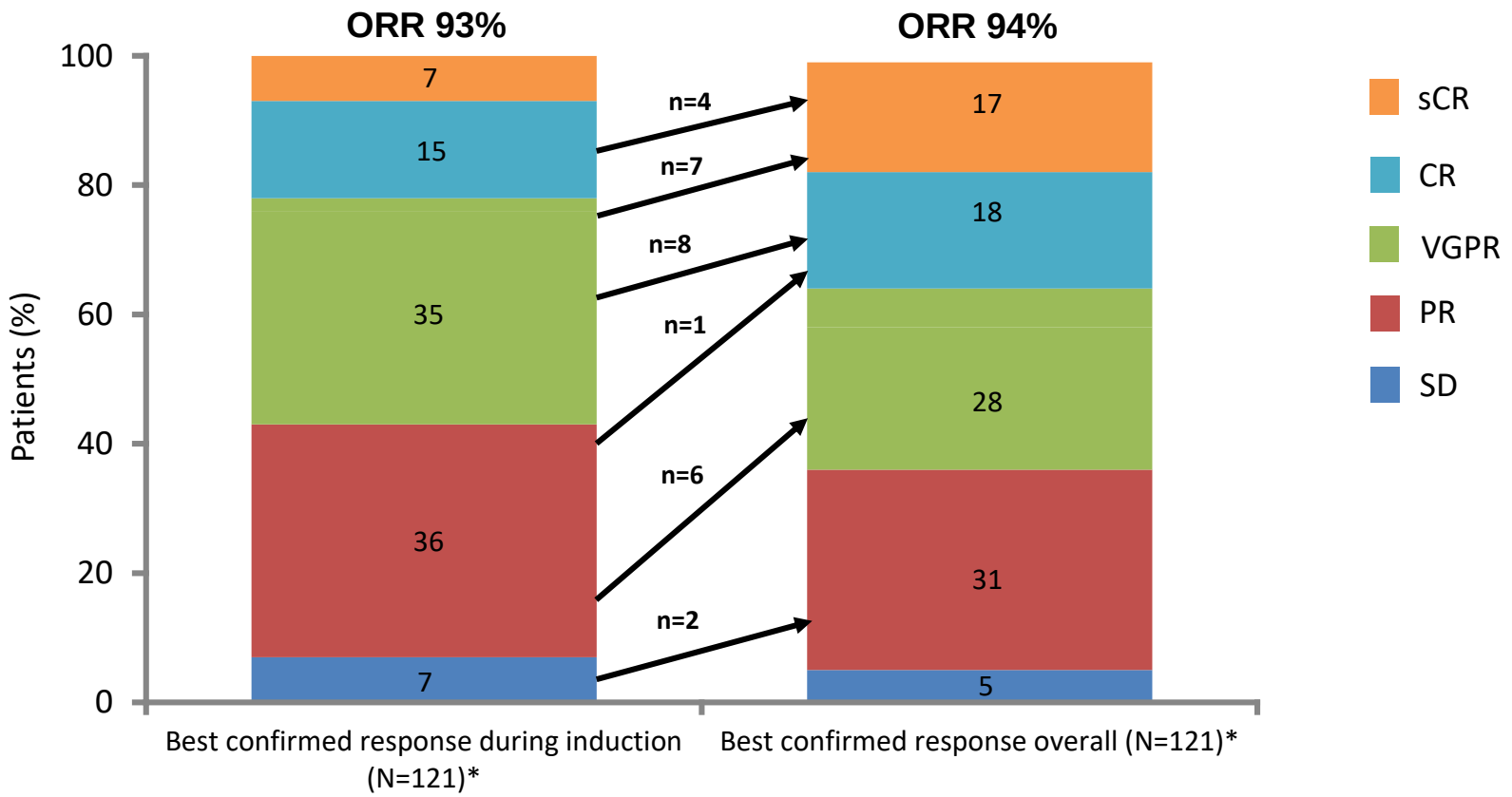
Ultra-high risk: HR 0.38



- **High risk - presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q).**
- **Ultra-high risk - presence of more than one lesion.**
- **Standard risk - absence of any of the above lesions.**

Jackson et al ASH 2017

Ixazomib Maintenance Therapy in Non Transplant Patients : integrated Analysis of Four Phase ½ Studies



- **28 (23%) patients improved their response during ixazomib maintenance:**
  - 4 CR to sCR, 7 VGPR to sCR, 8 VGPR to CR, 1 PR to CR, 6 PR to VGPR, and 2 *de novo* responses (SD to PR)

Dimopoulos et al ASH 2017

Phase II Study of Ixazomib with Lenalidomide Maintenance Following ASCT in Multiple Myeloma

- Ixa/Len (10mg daily with Ixa 3mg d1,8,15) as maintenance therapy post upfront ASCT
- ORR: ≥ 90% VGPR of and 81% estimated 2-year PFS
- 29 pts (45%) improved best overall response from post transplant baseline
- 8 of 14 patients with high risk disease progressed.
- peripheral neuropathy was limited to grade 1/2 and 6 grade 3 events
- Hematological adverse events were manageable with dose reductions

Patel et al ASH 2017

Phase II Study of Lenalidomide-Elotuzumab maintenance post- ASCT in Multiple Myeloma

- Lenalidomide-elotuzumab is a well tolerated maintenance therapy
- 36% of patients achieved improvement in quality of response while on therapy
  - 20% have converted to sCR/CR
  - Combined effect of AuSCT + lenalidomide-elotuzumab
- The number of patients achieving CR may be underestimated due to elotuzumab interference with electrophoretic measurements
  - 19 of 33 patients not achieving CR had GK paraproteins
- Additional follow up is required to determine if the improved quality of responses translates into improvements in PFS and OS

Thomas et al ASH 2017

Treatment of Myeloma Complications

1. Bone disease and hypercalcemia-intravenous bisphosphonates: Zoledronic acid; Targetting **RankL:Denosumab especially with renal dysfunction**
2. Hyperviscosity-IgM, IgG3; plasmapheresis as adjunct.
3. Recurrent infections-IV Ig only for recurrent life threatening infections.
4. Renal failure: hypercalcemia, myeloma kidney, hyperuricemia, IV urography, dehydration, plasma cell infiltration, pyelonephritis, amyloidosis.
5. Cardiac failure: amyloid, hyperviscosity, anemia.
6. Anemia: BM tumors, renal dysfunction, myelosuppression, low endogenous erythropoietin.
7. Neuropathy: sensory ± motor, amyloid, anti-myelin Ab.
8. Thrombosis: disease and/or therapy related

Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Relapse 1-3 prior therapies: Triplets preferred

Active In Len and Bort refractory MM

Kyprolis Pom Dex (no neuropathy)

Dara Pom Dex (deep responses)

Activity in Len refractory MM unknown:

Elotuzumab/Len/Dex (indolent relapse), Ixazomib Len/Dex (all oral), Kyprolis Len/Dex (no neuropathy), Dara Len dex (MRD- responses)

Activity in Bort refractory MM unknown:

Pom Bort/Dex, Dara Bort Dex (MRD- responses)

Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Doublets (frail patients): Pomalidomide/Dex (oral) or Kyrpolis/Dex (high risk, renal dysfunction, no neuropathy)

Multiply relapsed therapy:

Daratumumab alone or in combination (high risk), Panobinostat/Bort: Bort refractory

Targeted and Immune Therapy Protocols

Pomalidomide Cytoxan Dex (PCD) for relapse MM after Lenalidomide Bortezomib Dex (RVD)

- The all oral combination of pomalidomide 4mg d1-21, cyclophosphamide 300mg d1,8,15,22, and dexamethasone 40mg d1-4 and 15-18 treatment at first relapse following lenalidomide, bortezomib and dexamethasone, with or without ASCT, achieves **85% ≥ PR after 4 cycles**

- Toxicity is mostly hematological and manageable

- 94% (45/48, arm A) of transplant naive patients could proceed to a first ASCT after 4 courses of PCD following first relapse post RVD

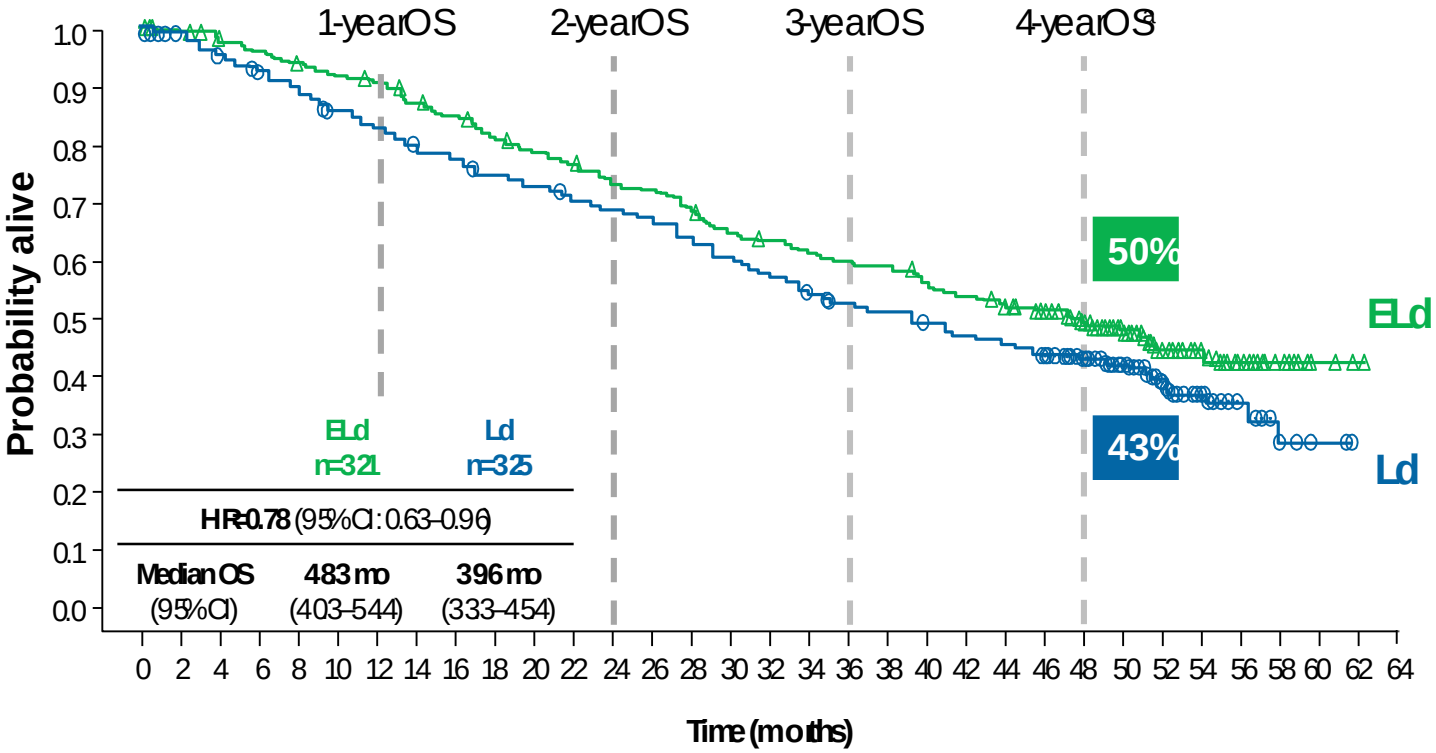
Gardaret et al ASH 2017

Final Analysis of Phase 3 Kyprolis Lenalidomide Dex (KRD) vs RD ASPIRE Trial: Overall Survival

- KRd demonstrated a statistically significant and clinically meaningful reduction in the risk of death vs Rd, improving median OS by 7.9 months (48.3 vs 40.4 months; HR, 0.79, *P*=0.0045)
- The KRd efficacy advantage is most pronounced at first relapse, with an 11-month improvement in median OS (47.3 vs 35.9 months; HR, 0.81)
- Treatment with KRd did not compromise OS after relapse

Stewart et al, ASH 2017

Overall Survival: Elotuzumab Lenalidomide Dex (Rd) vs Rd in Relapsed MM

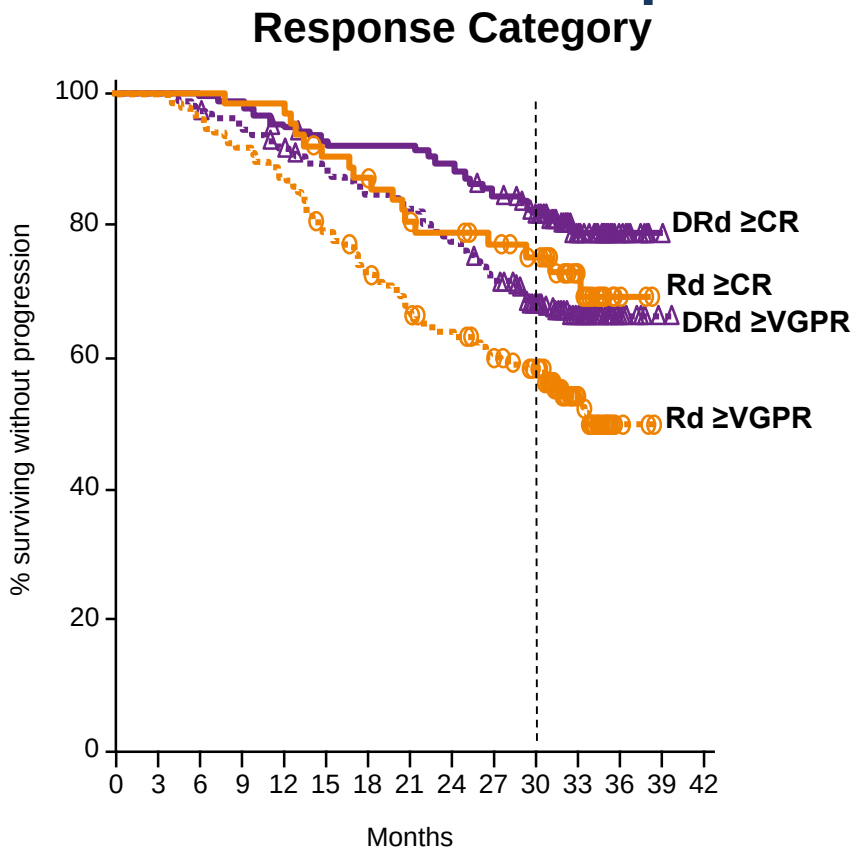


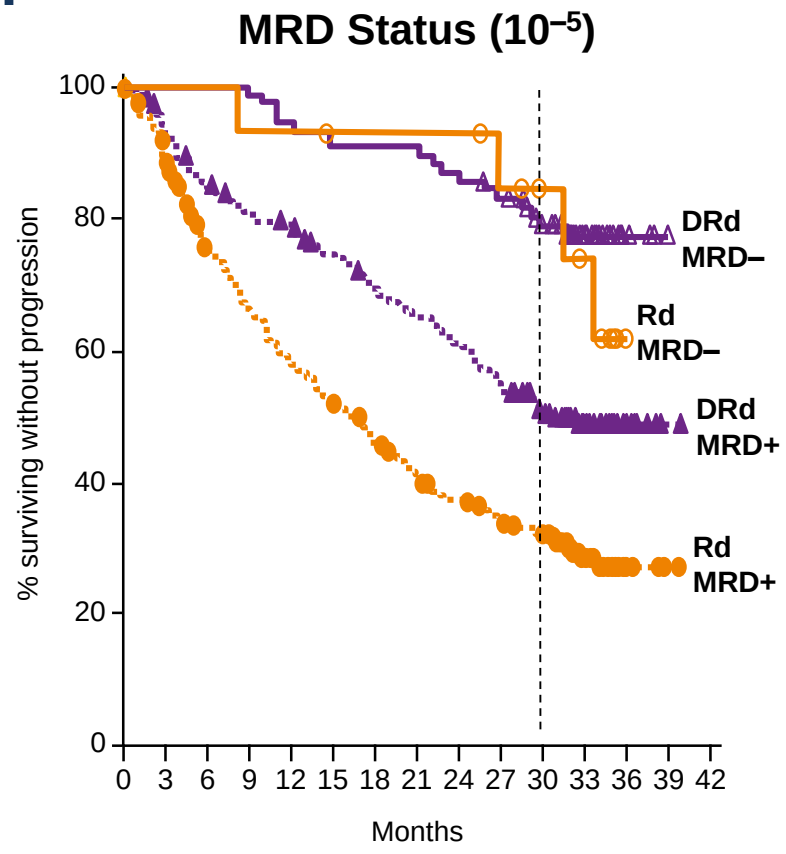
Patients at risk

ELd	321	313	298	287	278	264	255	243	232	228	222	213	208	202	193	184	174	164	158	154	147	141	137	128	109	80	53	42	24	10	4	2	0
Ld	325	312	298	287	278	264	255	243	237	228	222	213	208	202	193	184	174	164	158	154	147	141	137	128	109	80	53	30	13	7	3	0	0

Dimopoulos et al, EHA 2017

Daratumumab Lenalidomide Dex (DRd) vs Rd: PFS by Depth of Response





- Deeper responses were more common on DRd and were associated with longer PFS
- MRD negativity was associated with longer PFS

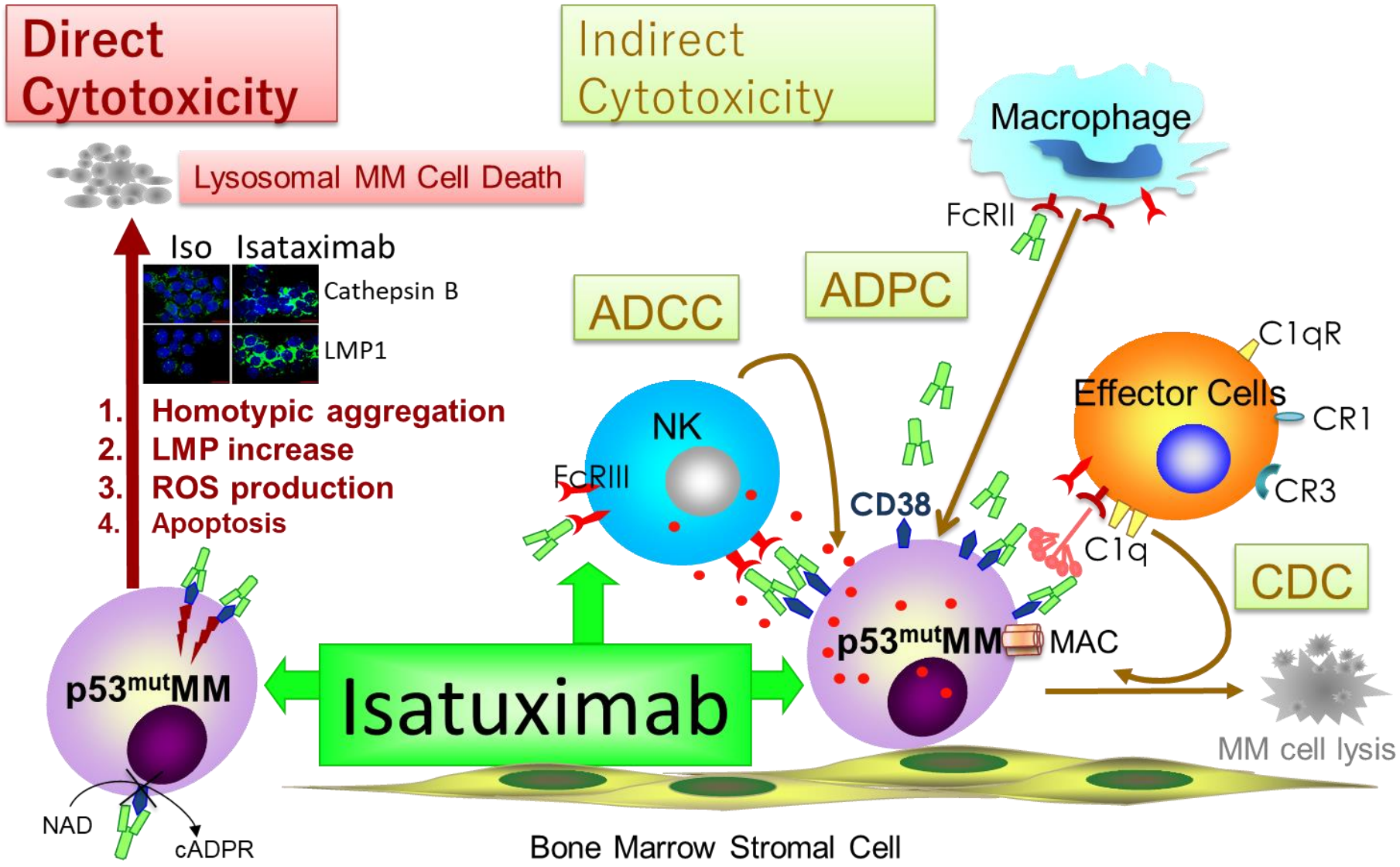
Dimopoulos et al ASH 2017

Subcutaneous Daratumumab in Relapsed or Refractory Multiple Myeloma (RRMM): PAVO, an Open-label, Multicenter, Dose Escalation Phase 1b Study

- DARA co-formulated with recombinant human hyaluronidase (DARA SC) enables dosing in 3 to 5 minutes
- DARA SC 1,800 mg achieves greater maximum C_{trough} compared with standard IV dose at C3D1
- DARA SC was well tolerated
  - Rate of IRRs with DARA SC was 12%; IRRs for DARA IV range between 45%-56% in RRMM[1-6]
- Clinical responses with DARA SC were observed, with rates similar to DARA-IV
- Ongoing phase 3 studies evaluating DARA SC 1800 mg

Chari et al ASH 2017

Isatuximab Triggers ADCC, ADPC, CDC, and Lysosomal MM Cell-Death



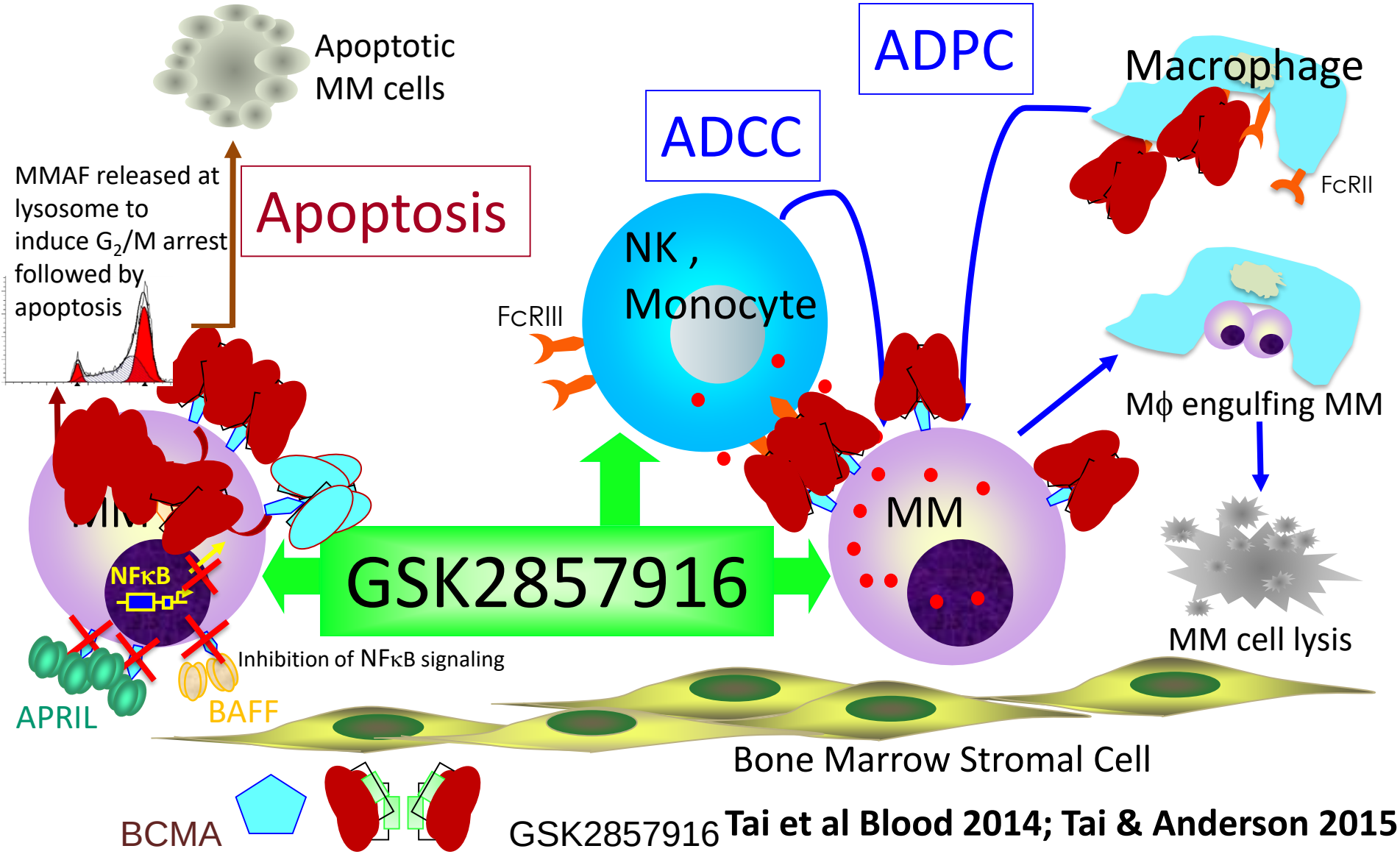
Tai et al Leukemia 2016;30:399

Isatuximab + Pom/Dex in RRMM TCD14079 Phase 1b

- **Acceptable and manageable safety profile.**
- **Isatuximab PK parameters not affected by Pom**
- **ORR 60%; ORR with isatuximab 10 mg/kg 61.3%. ORR in IMiD-refractory patients 54.1%.**
- **MTD for combination not reached**
- **A Global Phase III study of isatuximab plus Pom/dex in RRMM patients ongoing (NCT02990338).**

Richardson PG., et al. Abs #1887, ASH 2017

A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects



Tai et al Blood 2014; Tai & Anderson 2015

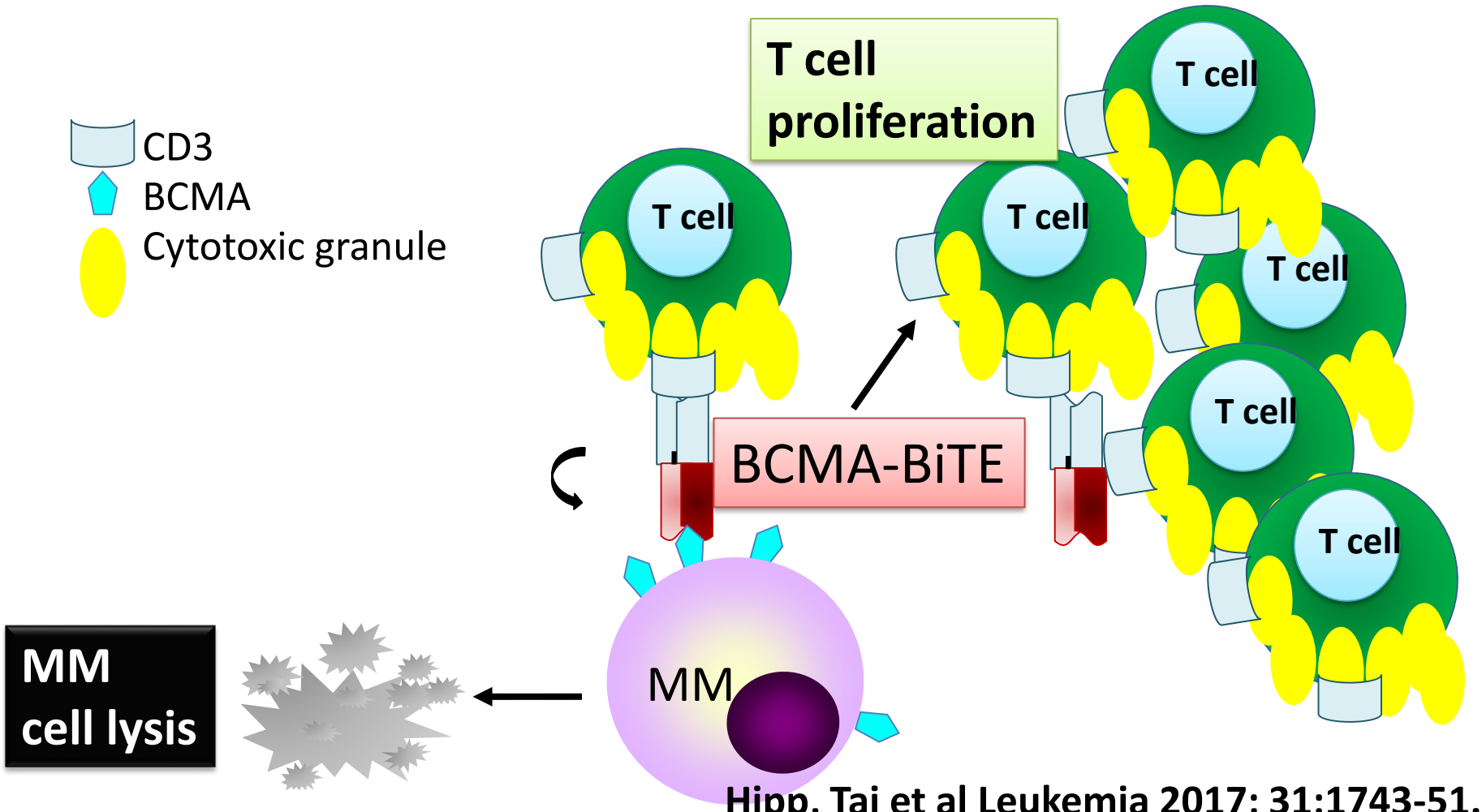
GSK2857916 Aurostatin Immunotoxin Targeting BCMA in Relapsed/Refractory Multiple Myeloma

- Median follow-up 6.6 months; study is ongoing
- ORR of 60% in heavily pre-treated MM
  - 51% of patients in Part 2 had VGPR or better
- Median PFS 7.9 months
- Well tolerated and side effects manageable
  - Thrombocytopenia and corneal events most frequent AEs
  - IRRs occurred in only 23% of patients without pre-medication; no IRRs occurred on subsequent infusions
- Additional monotherapy and combination studies are planned

Trudel et al ASH 2017

DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response

BCMA-BiTE-based Immunotherpaies

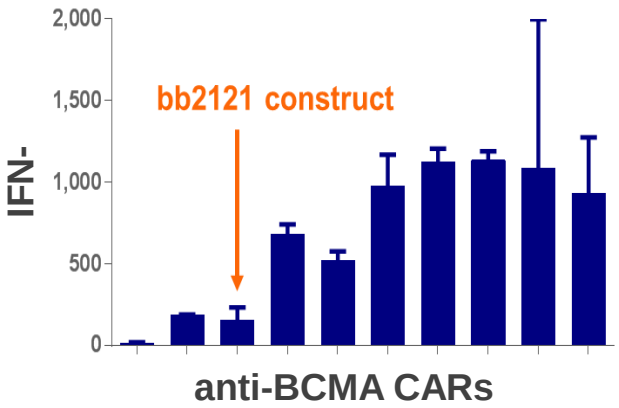


Hipp, Tai et al Leukemia 2017; 31:1743-51.

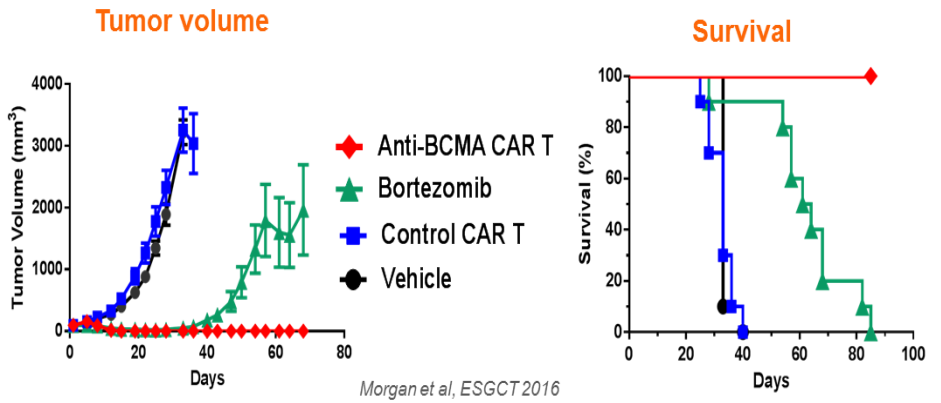
bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product Candidate Berdaja et al ASH 2017

- bb2121 is autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3ζ T cell activation domain
- Construct demonstrated potent preclinical *in vivo* activity with low tonic signaling

bb2121 demonstrates low antigen-independent signaling

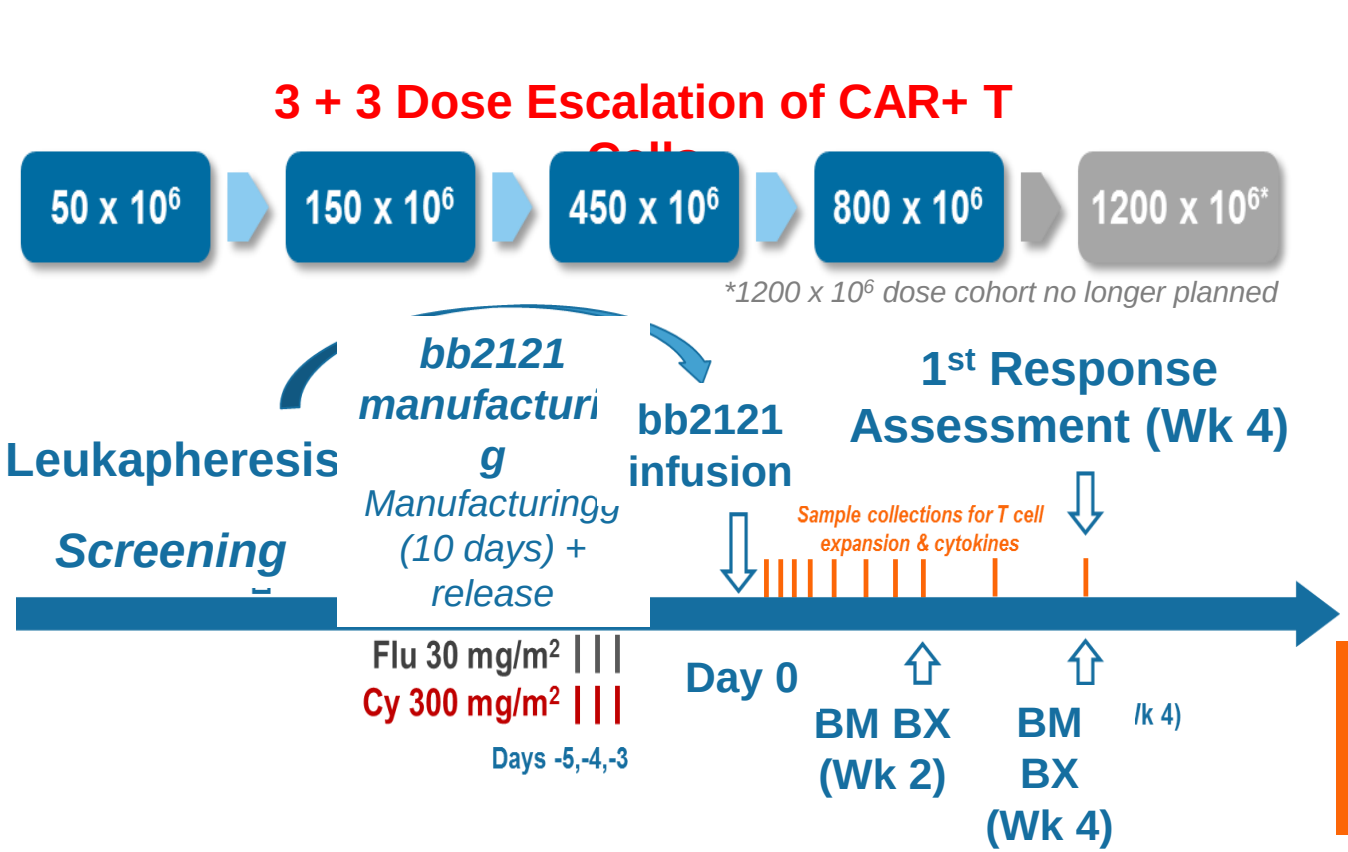


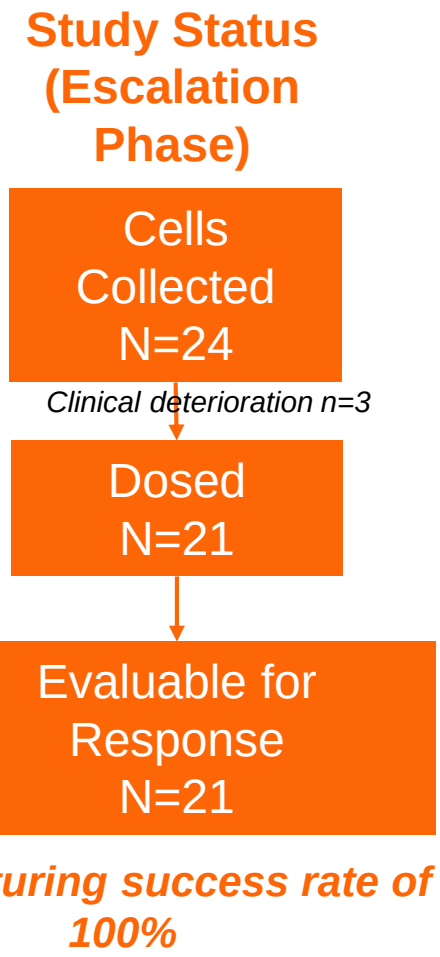
bb2121 improves survival and drives tumor clearance in MM mice



Morgan et al, ESGCT 2016

Clinical Trial of bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product





Manufacturing success rate of 100%

Berdeja et al ASH 2017

Conclusion : b2121 Demonstrates Deep and Durable Responses with Manageable Safety Profile

bb2121 at active doses (150 – 800 × 10^6 CAR+ T cells)

94% ORR, 89% VGPR or better, 56% CR or better

- Median PFS not reached with follow up of 40 weeks
- MRD negative results in 90% of MRD evaluable patient samples
- Disease progression in 4 patients; 3 of 3 evaluable patients remain BCMA positive at progression

bb2121 manageable through doses as high as 800 × 10^6 CAR+ T cells

- The 2 reported events of grade 3 CRS resolved within 24 hours
- 1 case of delayed onset, reversible grade 4 neurotoxicity associated with tumor lysis syndrome and CRS
  - Patient with highest tumor burden on the trial
  - Rapid myeloma response (VGPR) in tumor with low BCMA expression (1% of plasma cells)

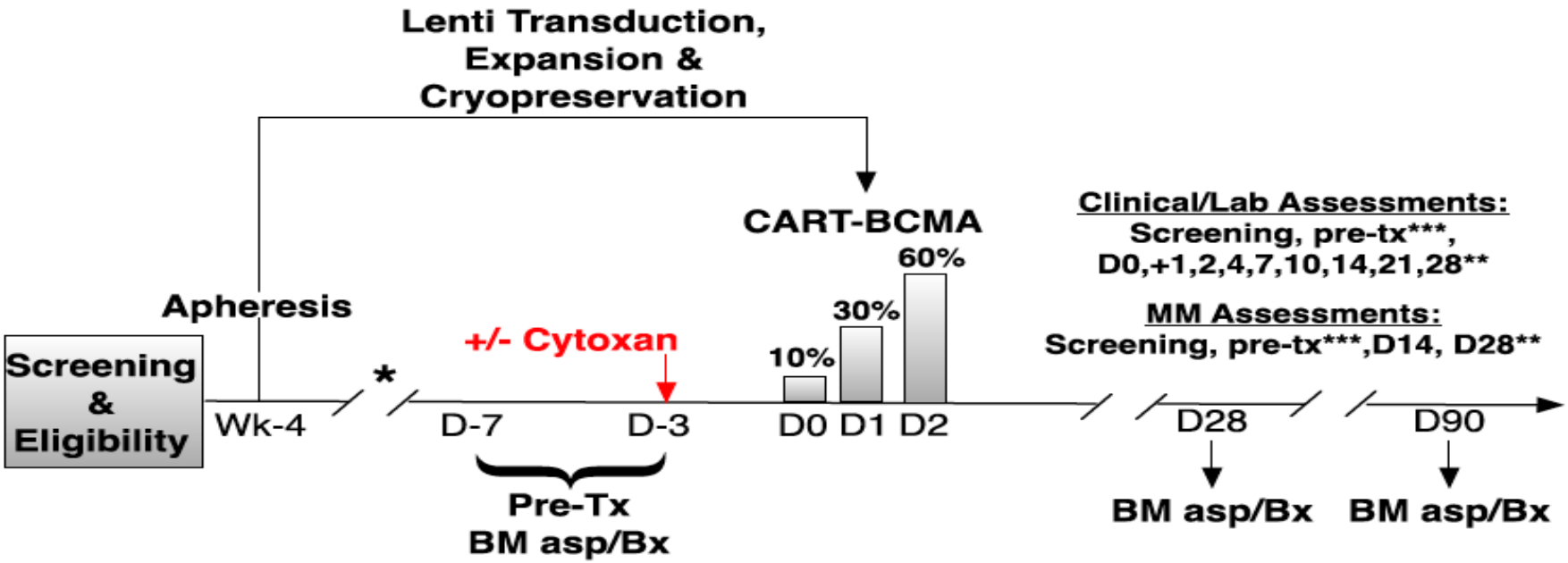
Global Pivotal Trial (KarMMa) is open for enrollment

- bb2121 dose range: 150-300 × 10^6 CAR+ T cells

Berjada et al ASH 2017

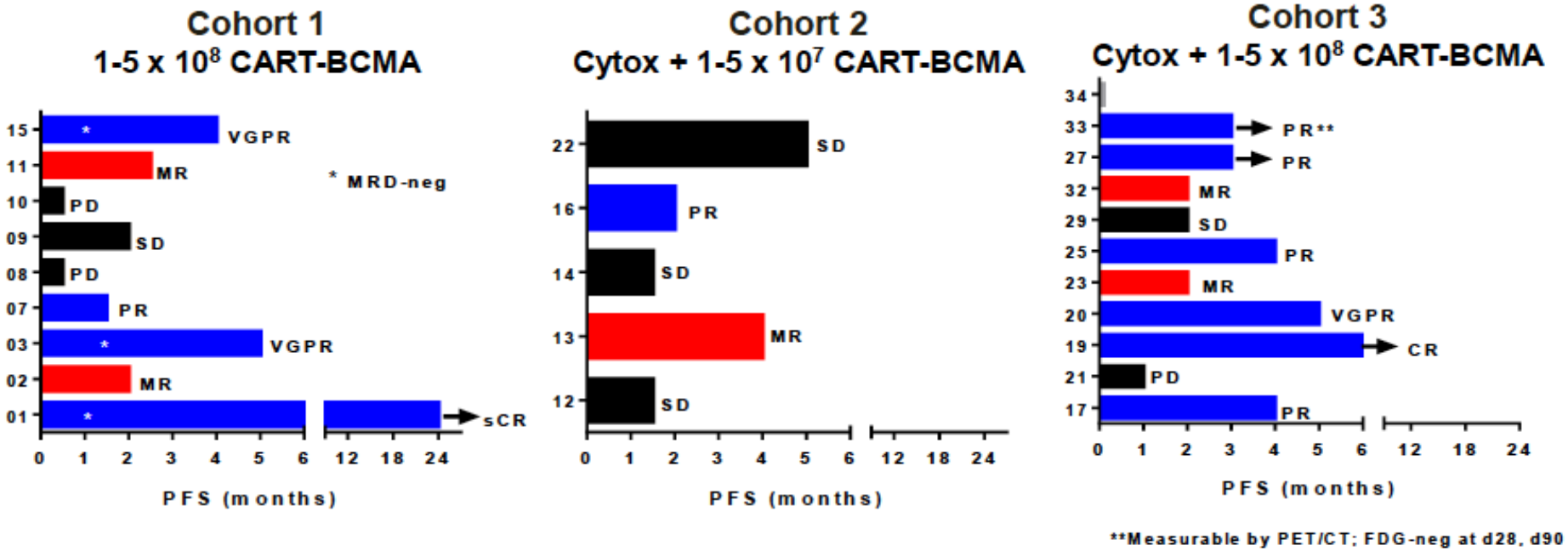
BCMA CAR T After Cyclophosphamide Conditioning in Relapsed Refractory MM

Study design



* Patients may receive therapy during manufacturing to maintain disease control
** After first 28 days, follow-up is q4 wks up to 6 mos., then q3 mos. up to 2 years
*** Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion

Clinical activity



ORR (≥PR) = 11/24 (46%)

- **≥MR = 16/24 (67%)**

ORR (≥PR) @ 10e8 = 10/19 (53%)

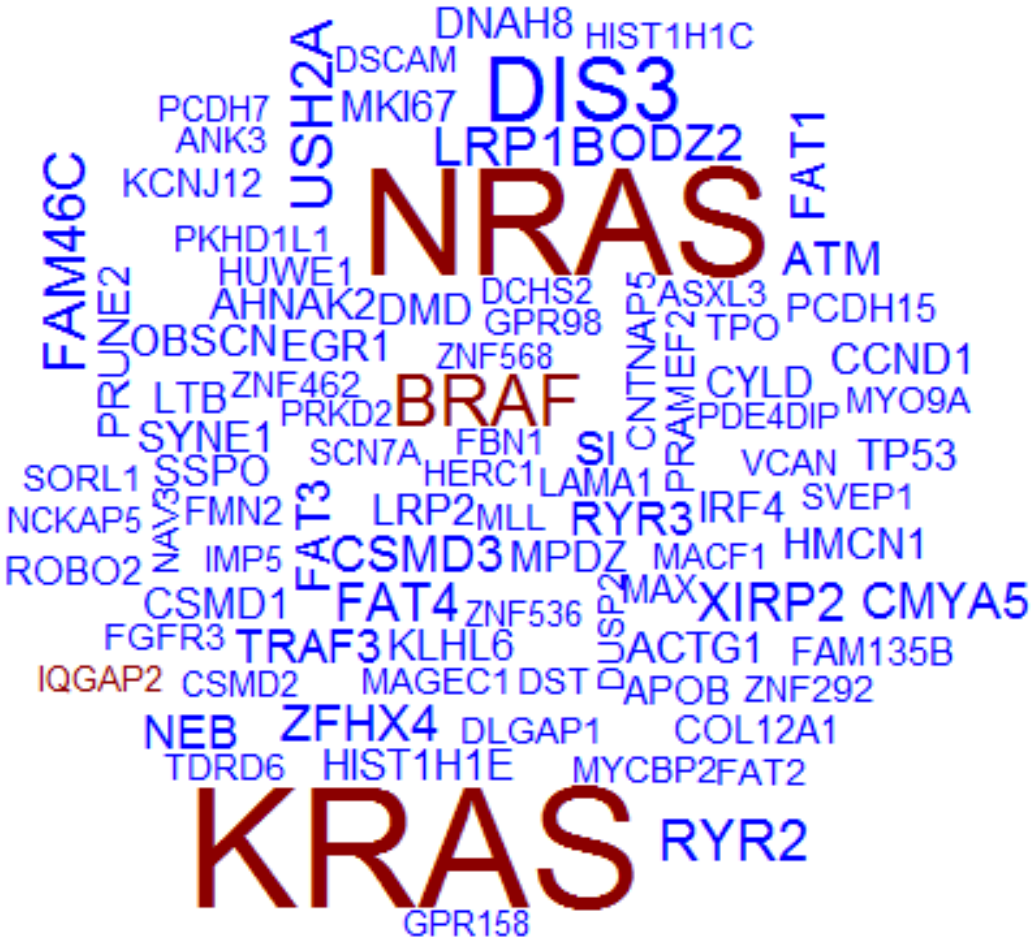
Median DOR = 4 months

Cohen et al ASH 2017

Conclusions

- **CART-BCMA has activity in heavily pre-treated MM**
- **Lymphodepletion is not required for robust expansion and response**
- **Cyclophosphamide may increase frequency of patients with strong expansion**
- **CART-BCMA detectable by qPCR up to 21 months**
  - typically 4-6+ months
- **Toxicities remain CRS and neurotoxicity**
  - No increased toxicity with cyclophosphamide
- **Responses: ≥PR in 11/24 (47%)**
  - 4 ongoing at 3+, 3+, 6+ and 24+ months
  - 1-5 x10^8 dose more active
  - Not clearly associated with baseline BCMA expression or sBCMA concentration
- **Decreased BCMA expression may be escape mechanism**

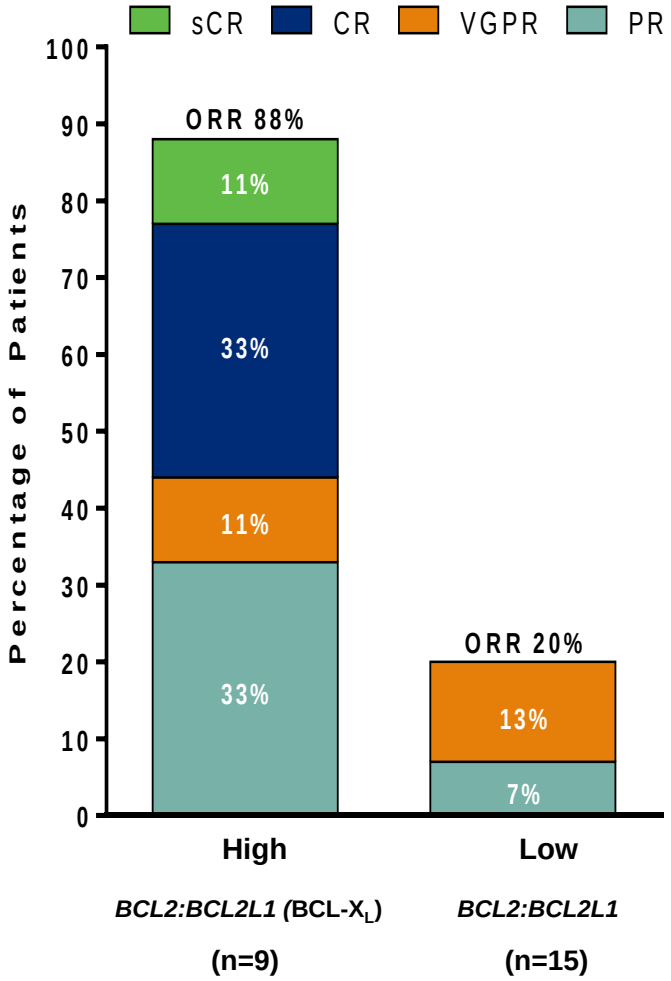
Mutational Landscape or Cloud of Myeloma

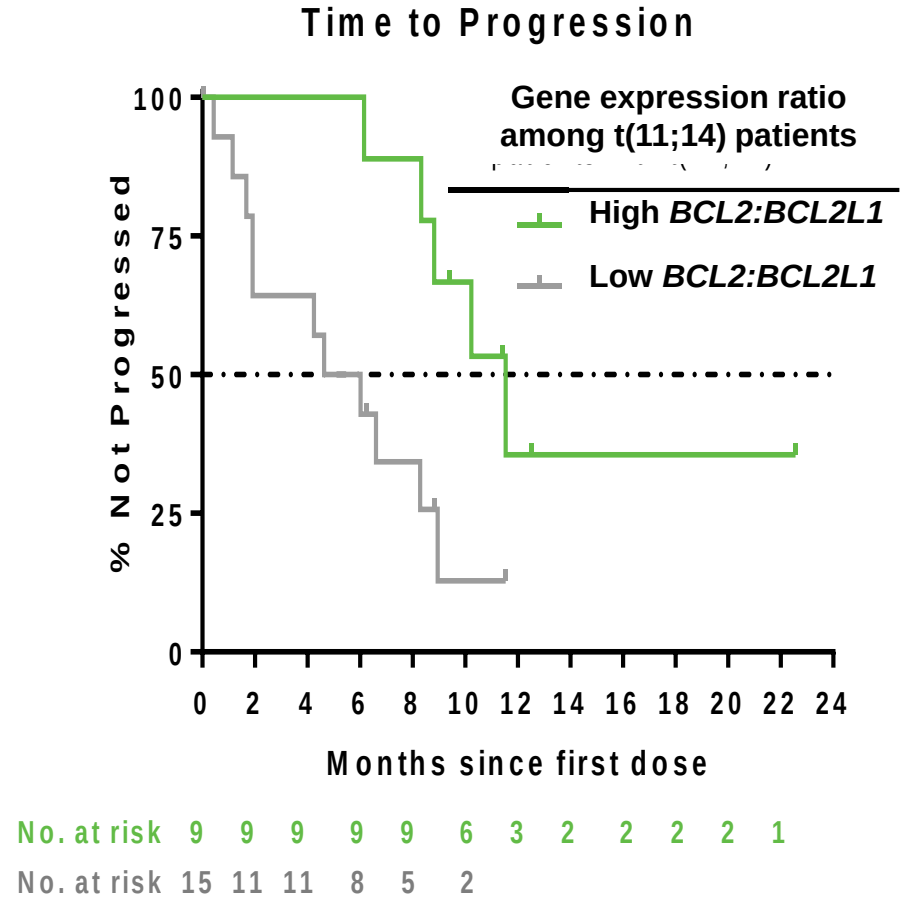


Therapies Targeting Ras Raf MAPK Pathway Achieve Transient Responses

Morgan GJ, Walker BA and Davies FE. Nature Reviews Cancer. 2012 Chapman *et al* Nature Genetics 2011, Walker et al 2012 Blood, Lohr et al Cancer Cell 2014, Bolli et al Nat Comm 2014, Walker BA et al Nat Comms 2015

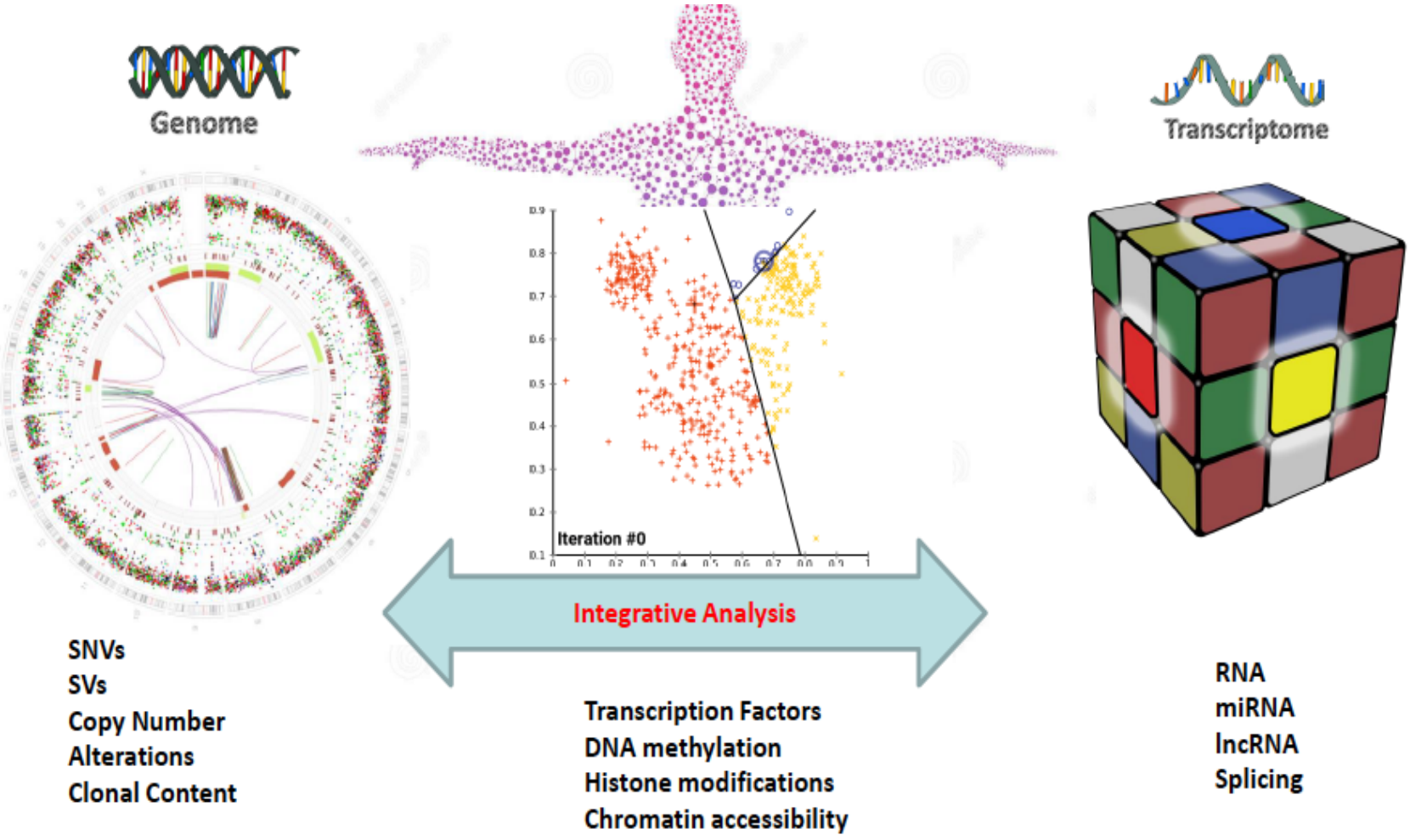
Responses to Venetoclax (Target BCL-2) by *BCL2:BCL2L1* Ratio Among t(11;14)-Positive Patients with RRMM





Kumar et al, ASH 2016

Integrative Oncogenomic Analysis: Combining Whole Genome, Transcriptome, and Epigenome Identifies Altered Chromatin Accessibilitiy Landscape and New Targets in Multiple Myeloma



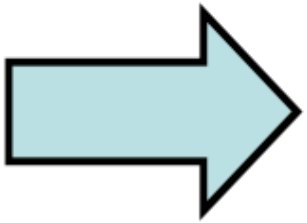
Szalat et al ASH 2017

Conclusions

1. We have analyzed the open chromatin landscape in MM and identified myeloma signatures

2. The integration of epigenomic and genomic data reveals:

- High number of mutations in regulatory regions
- Epigenomic profile is impacted by mutations in promoter/enhancer regions
- Expression changes are influenced by epigenomic dysregulation and chromosomal structural variants

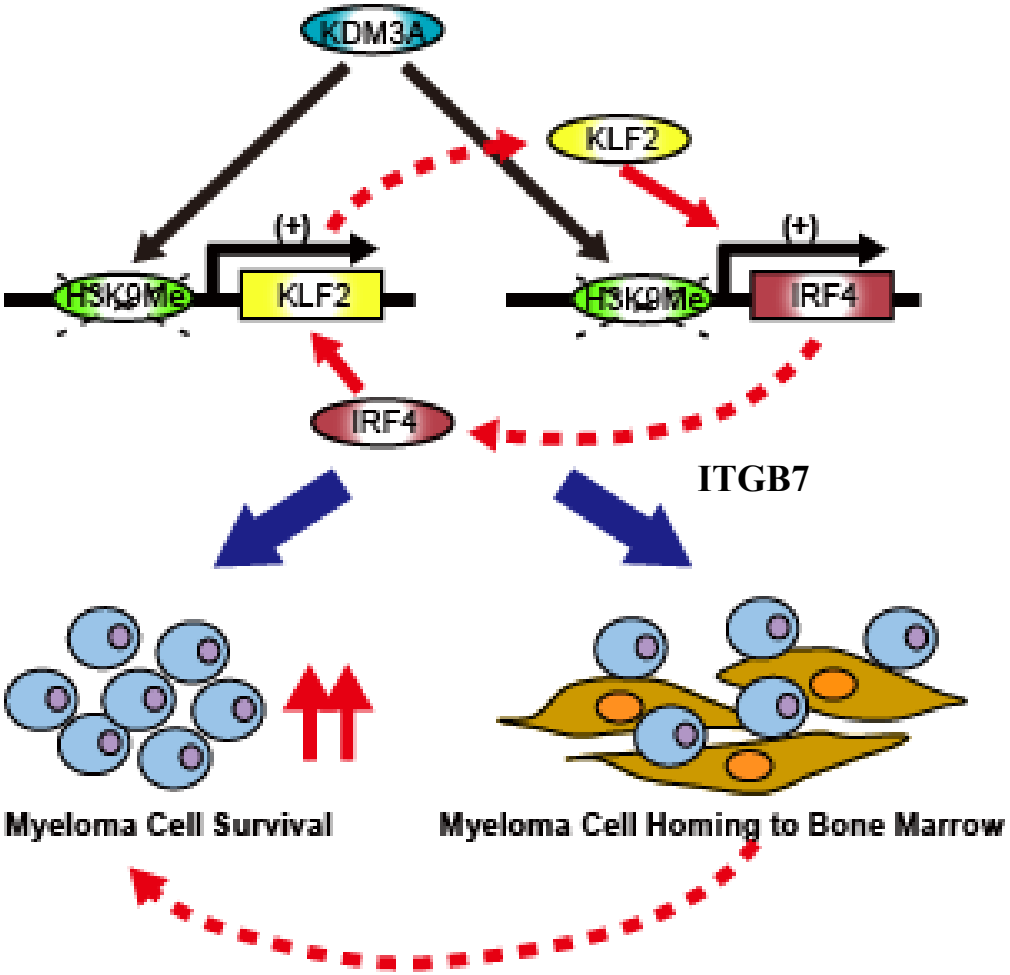


We are validating new potential therapeutic targets

Szalat et al ASH 2017

Model of KDM3A-KLF2-IRF4 Axis in MM cells

KDM3A catalyses removal of H3K9 mono- and di-methylation in MM



Ohguchi et al Nat Comm 2016; 7:10258

cfDNA Allows Discovery-Oriented Sequencing in MM Patients

- Discovery-oriented low-pass WGS and WES is possible from cfDNA in MM
  - Requires sufficient tumor fraction
  - Cost-effective markers predict efficiency of cfDNA sequencing
- cfDNA is an excellent proxy for clonal events in BM of MM patients
- cfDNA and BM may reveal distinct subclonal information
- cfDNA is useful as a marker for disease progression and clonal evolution
  - Potentially useful for non-secreting MM

Summary and Conclusions

- Clinical trials of novel targeted and immune agents to delay or prevent progression of SMM.
- In newly diagnosed patients, triplets are standard of care, with doublets only in frail patients, and four drug regimens now being evaluated.
- Maintenance with lenalidomide is standard, proteasome inhibitors and combinations in high risk MM
- ASCT remains standard of care; double transplant in high risk MM
-

Summary and Conclusions

- Triplets achieve increased extent and frequency of response, PFS, and OS in relapsed MM
- Daratumumab and isatuximab combinations, BCMA immunotoxins, and BCMA CAR T cells achieve deep responses
- Venetoclax in MM with t (11:14) and high Bcl-2 gene expression is an example of personalized medicine in MM .
- Future studies will integrate genomic and epigenomic signatures, and probe PB, ie cell free DNA (cfDNA) versus BM

Future Directions

Combination therapies defined in preclinical studies will be used to treat subsets of patients, defined by profiling and informed by biomarkers

Collaborative effort of academia, biotech/pharma, NIH/NCI, FDA, and advocacy- International Myeloma Society-will facilitate continued advances.

Long term disease free survival and potential cure of MM will require both 1. achieving minimal residual disease negativity, and 2. combined immune therapies to restore host immunity.

Case 1

A 50 year old man who is asymptomatic is found at the time of a routine physical exam to have elevated total protein and IgG lambda of 2.5 gm/dL. Hct 47%, Creat 1.0mg/dL, and Ca 9.0mg/dL
BM 20% plasma cells FISH t(11;14), and serum kappa:lambda 2.3.
Bone survey normal and MRI reveal no bone disease.

What is the diagnosis and what would you do now?

1. Smoldering MM at low risk of progression, follow expectantly off all therapy
2. Smoldering MM at intermediate risk of progression, consider clinical trial
3. Smoldering MM at high risk of progression, treat with lenalidomide, bortezomib, and dexamethasone
4. Active MM, treat with lenalidomide/bortezomib/dexamethasone, stem cell harvest, and lenalidomide maintenance until progression
5. Active MM, treat with lenalidomide/bortezomib/dexamethasone, stem cell harvest, high dose therapy/stem cell transplant, and lenalidomide maintenance until progression

CASE 1

The correct answer is choice 1.

There is no hypercalcemia, renal dysfunction, anemia, or bone disease, nor is there a defining event (<60% bone marrow plasma cells, kappa:lambda >100 fold abnormal or bone disease on PET/CT or MRI) to make this active multiple myeloma (MM). It is not monoclonal gammopathy of undetermined significance (MGUS, <3gm M protein, <10% BM plasma cells) due to 20% BM plasma cells. It is smoldering MM (SMM, ≥ 3gm monoclonal protein or ≥ 10% BM plasma cells without MM defining event). Within SMM, risk factors for progression to active MM include monoclonal protein ≥ 3g/dL , ≥ BM10% plasma cells, and kappa:lambda <0.125 or >8. Risk of progression is low, intermediate, and high with 1 of 3, 2 of 3, and 3 of 3 of these criteria, respectively. This patient has a low risk of progression, and therefore should be followed expectantly off all therapy, with monitoring every 3 months of the myeloma profile (serum protein electropheresis, kappa:lambda). Patients with intermediate and high risk of progression to active MM are eligible for clinical protocols of novel targeted and/or immune agents to delay time to progression to active MM.

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548

Case 2 2Case 2

A 37 year old man presented with back pain and fatigue.
Hct 30%, Creat 2.3mg/dL, Ca 8.0mg/dL , and compression fracture at L3-4 Serum IgG lambda 8.5gm/dL, BM 80 % plasma cells with FISH del 17p. He is treated with lenalidomide bortezomib dexamethasone, high dose melphalan and ASCT, followed by lenalidomide/bortezomib maintenance. Relapse occurs 6 months later with rising IgA M protein and new bone disease.

Optimal therapy at this time would be:
1. Carfilzomib lenalidomide dexamethasone
3. Ixazomib lenalidomide dexamethasone
3. Elotuzumab lenalidomide dexamethasone
4. Carfilzomib pomalidomide dexamethasone
5. Daratumumab lenalidomide dexamethasone

CASE 2

The correct answer is choice 4. This gentleman presented with high risk multiple myeloma (MM) by virtue of his deletion 17p and was treated due to anemia, bone disease, and renal dysfunction with lenalidomide bortezomib dexamethasone induction, high dose melphalan and stem cell transplantation, and then lenalidomide and bortezomib combination maintenance post transplant. Although lenalidomide is FDA approved as maintenance until progression posttransplant due to prolongation of PFS and OS, the benefit is predominantly in standard risk MM. Nooka et al have shown that bortezomib and lenalidomide can decrease the rate of early relapse that is characteristic of high risk myeloma, and clinical trials of lenalidomide, ixazomib, lenalidomide and ixazomib, lenalidomide and elotuzumab maintenance therapy are ongoing to assess their impact, especially in high risk MM.

Nooka et al Leukemia 2014; 28: 690-3.

(continued)

CASE 2

This relapse of disease occurred while patient was receiving lenalidomide and bortezomib therapy, and MM is therefore resistant to these agents. Second generation immunomodulatory agent pomalidomide combined with second generation proteasome inhibitor carfilzomib is therefore the most reasonable option. The other choices include either carfilzomib, ixazomib, elotuzumab, or daratumumab, in each case combined with lenalidomide dexamethasone; they were all FDA approved based upon randomized trials in relapsed MM when compared to lenaliodmide dexamethasone, and were done in the setting of relapsed, but lenalidomide sensitive, MM. The activities of these regimens in lenalidomide and bortezomib refractory MM, as in this patient, is unknown.

Stewart et al NEJM 2015;372:142.
Moreau et al NEJM 2016;374:1621.
Lonial et al MEJM 2015;373:621.
Lokhorst et al NEJM 2015;373:1207.
Palumbo et al NEJM 2016;375:754.
Dimopouos et al NEJM 2016;375:1319.
Chim et al Leukemia 2018;32:252.